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THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 50/NUMBER 1 JANUARY–FEBRUARY 1983

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
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Profile of Congressional Health Legislative Aides

JOHN T. GRUPENHOFF, PH.D.

Abstract

A detailed survey undertaken to determine the characteristics and work patterns of congressional legislative aides (LA's) who handle legislation on health (including medical care and biomedical research) has indicated that LA's are generally young, predominantly female, very well educated, and experience high turnover rates. Only 2% have been trained in the health professions, and the rest have limited scientific educations. On the average, LA's are responsible for more than four issue areas other than health, and also must handle constituent inquiries. Stressed for time and pressured by rapidly moving legislative situations, they average less than 10 hours weekly on health legislation, and less than 2 hours per week in direct contact with their legislators about it.

This study raises important questions about whether—and how—the biomedical research and health care community can deal with the problems inherent in this situation, and can communicate best with LA's about important legislative issues.

Those who seek to influence the U.S. Congress about medicine and health policy matters frequently find it necessary to deal extensively with staff assistants to senators and representatives on the particulars of the legislation or program involved. Although the initial contact concerning a problem or opportunity may be with a member of Congress, in person or by other communication, it is nearly always the case that a legislative aide will fully define the matter, discern its implications, and develop a suggested approach for presentation to the legislator.

This work pattern has developed out of necessity, because from the early 1960s the Congress has worked under ever-increasing legislative workloads and constituent requests for assistance. The number of laws passed (laws which then must be revised and amended from time to time), the number of days spent in session, the number of committee hearings, the amount of time spent in the oversight of federal regulations coming from the agencies, and the volume of constituent communications have all increased greatly.

Also, since 1965 the Congress has believed itself to be at a competitive disadvantage in relation to the executive branch in terms of information about federal programs and other matters of concern, such as the budget and the economy. Frequent clashes with presidents about the Vietnam war and subsequently about the size and shape of government efforts have caused the Congress to seek ways to improve its situation.

In response, the Congress rapidly increased its staff. Since 1965, personal staff (both in Washington and in district offices) and professional committee staff have doubled. Staff to individual members now exceeds 12,000; the professional committee staff exceeds 3,000. Increasing staff workloads have produced specialization. There are now office managers, administrative assistants, media aides, caseworkers, and legislative aides who have responsibility for specific issue areas, among others.

The Legislative Aide for Health Legislation

In the office of nearly every member of Congress there is an aide who has responsibility for handling health legislation, who is hired by, paid by, and directly responsible to the individual legislator. This group of aides exercises considerable influence in shaping the attitudes and opinions of members of Congress on health issues. The

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characteristics and work patterns of these aides (LA's) are the subject of this study.

An LA may work either for a legislator who is a member of one of the three Senate health committees or subcommittees (38 members total) or of the three House subcommittees (38 members total),[*] or for a legislator who is not a member of one of those committees or subcommittees. This study revealed that the characteristics and work patterns of the two groups vary considerably, and data is presented differentiating the two groups.

There is another, very important, group of health legislative staff that is not included in this study. These are the professional staff members of the committees and subcommittees, where the major questions of health policy are hammered out prior to floor action. Without question, these professionals hold considerable decision-making power at the staff level. They are usually long-term congressional employees, experienced in the issues and politics of concern to committee members. For the committees, the professionals frequently define the issues for discussion, staff the hearings, aid in the "markup" of bills, and write the committee report drafts. A study is now under way, similar to the present study, on such professional committee staff.

Methods

The survey took place between July 11 and August 5, 1982, a four-week period chosen because the Congress would be in session, because the second session of the two-year 97th Congress would be in progress—by which time congressional staffs should have achieved maximum stability, and because it fell shortly before election campaigns began in earnest (campaigns distort normal working patterns).

Each of the LA's in the Senate (100) and House of Representatives (435) was called by telephone and asked to participate; 12 refused, and 10 could not be reached. A four-page, 38-question survey was prepared. There were 343 respondents to 513 questionnaires sent, a 67% response.

Results

The survey revealed the following characteristics and work patterns.

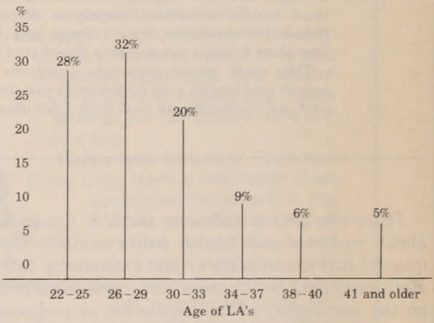
Age

Health LA's are, for the most part, young. Fully 60% are under age 29 and 95% are under age 40 (Table I). Among the 343 respondents, only four were in their 40's, four in their 50's, and four in their 60's.

Senate LA's averaged 1.7 years older than House LA's.

TABLE I

Age Distribution: Health Legislative Aides to Senators and Representatives, 1982



Education

The educational levels of the respondents were very high when compared to the national population. For example, 94% had an undergraduate degree, and 275 (51%) had gone on to graduate work; 122 (36%) had completed one or more graduate degree programs (Table II). (The Center for Educational Statistics, U.S. Department of Education, Hyattsville, Maryland, reports that 17.1% of the present population have undergraduate degrees, and that 21.3% in the 25–29-year-old population also do, the average level of education being 12.5 years.)

TABLE II

Educational Backgrounds of LA's
Percentage Completing Undergraduate and Graduate Work

	Overall		House	Senate
	No.	(%)	%	%
Undergraduate	319	(94)	93	98
Graduate	122	(36)	32	45

---

[*] The three Senate and three House counterpart committees are: Senate Finance Committee (Subcommittee on Health) and the House Ways and Means Committee (Subcommittee on Health); Senate Labor and Human Resources Committee (no subcommittee this Congress) and the House Energy and Commerce Committee (Subcommittee on Health and the Environment); and the Senate and House Committees on Appropriations (Subcommittees on Labor, Health and Human Services).

Of those completing *undergraduate* work, only 32 (6%) were science majors. Political science/government majors and those who majored in allied fields, such as public administration, international affairs, and history, totalled 51%. Nearly all others graduated with liberal arts and allied fields degrees, a considerable number having studied journalism or news media.

Overall, those with undergraduate degrees took 4.2 courses in science, indicating a level of scientific course work about equal to that of the average college graduate. LA's to House health committee members averaged 5 courses and those to Senate health committee members averaged 6 courses.

Of the 122 LA's holding *graduate* degrees, eight (7%) were from health fields. Two were M.D.'s, both serving as LA's to Senate committee members, and six held MA or equivalent degrees in health fields, including three with health committee senators (MPH, gerontology, and community organization/health care degrees), and two with House health committee members (one has a Family Nurse Practitioner degree, the other a health policy/women's issues degree), plus a nurse on a senator's personal staff. (There are at least seven more physicians and nurses serving as professional staff on the health committees.)

Of the remainder, 46 lawyers constituted the largest category (38%). There were 11 (9%) Ph.D.'s, in anthropology (1), psychology (2), English literature (1), and political science and allied programs (7). All others held MA-level degrees, most in political science and allied programs.

As can be seen, most formal education and training was in the *processes* of law, government, political science, and other fields, rather than in *specific policy* or *issues*, such as health, and only 2% had health professions training.

Experience

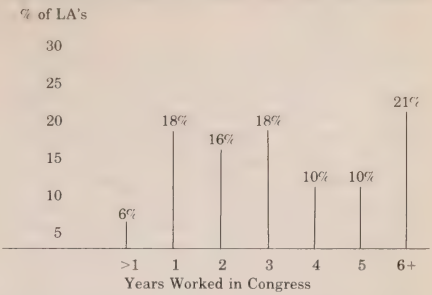
The effectiveness of an LA is enhanced by experience with congressional procedures and processes, especially those of the committees dealt with; by experience with and historical perspective on the specific legislation being considered; and by experience in using information sources within and outside Congress.

The survey queried how much experience LA's have (1) in full-time jobs in the Congress, (2) in previous comparable legislative jobs in the Congress, and (3) in their present positions.

First, total years spent in full-time posts in the Congress was recorded because many congressional jobs can aid the acquisition of experience: receptionist, caseworker, legislative analyst, media staff member. Forty per cent of LA's had worked less than two full years in Congress, and 79% had worked five years or less (Table III). Second, 56% had no previous congressional legislative experience, and 78% had no specific experience in health legislation. Third, the average number of months spent in the present job was 28.4, and 29% had held their current jobs for one year or less. LA's to health committee members had a slightly longer tenure than the average of LA's overall.

TABLE III

Years Worked in Congress, at Full-Time Posts, by LA's



Women/Men Ratio Among LA's

At the time of the survey, data taken from published lists of LA's showed that 58% of the LA's in the Senate were women, compared to 57% in the House. This represents a striking increase in the number of women in those posts since 1977 (see Table IV), when 35% of the Senate LA's and 46% of the House LA's were women (1).

The same trend was in operation for LA's to members of the Senate and House health subcommittees between 1977 and 1982, the number

TABLE IV

Percentage of Women LA's in the Senate and House 1977 through 1982

Year	Senate %	House %
1977	35	46
1978	41	49
1979	52	48
1980	53	52
1981	55	52
1982	58	57

of such women LA's increasing in the Senate from 48% to 62% and in the House from 37% to 50%.

Marital Status

Married LA's constituted 35% of all respondents (121), and of those married, 88% (106) had spouses working full time. Nearly half of the working spouses were employed in the Congress (23) or in federal agencies (20), probably providing reinforcing attitudinal and informational roles regarding congressional matters of interest.

Turnover Rates of LA's and Members of Congress, 1977 to 1982

The turnover rates for LA's, as well as members of Congress, have been massive in recent years. In the House of Representatives, for example, 95% of the LA's in 1982 were different from those in 1977, and in the Senate, 91% were different. However, simply tabulating the 1977–1982 changes does not tell the whole story, because many offices had several changes during that period. For example, in the 435 House offices, there were 888 changes of LA's from 1977 to 1982.

Also, in recent months the rate of turnover seems to have escalated. In the 18 months from the beginning of the 97th Congress in January 1981 to July 1982, when the survey was taken, 270 of 435 House LA's and 52 of 100 Senate LA's had changed.

The turnover rate of LA's to committee members was also large; only 2 of 38 LA's in the Senate and 3 of 38 LA's in the House were the same in 1982 as in 1977.

Also, the turnover rate among members of Congress in recent years has been considerable. When the 97th Congress convened in 1981, a majority of legislators had served five years or less, and three quarters of them had been newly elected since President Nixon's resignation in 1974.

This turnover in legislators and LA's has significant implications for congressional policy making on health matters, because continuity and institutional memory are vital to program stability.

Medicare and Medicaid, which were created in the Great Society Congress (1965–1966) and are by far the largest, most complex, and seemingly least controllable programs of that era, are a case in point. Only three members of Congress remain on the committees which developed this legislation in 1965, and only 13% of members of both the Senate and House who served in the Congress in 1965 are still there. However, *none* of the professional staff who served the committees which developed the legislation remain, and *none* of the LA's serving members of those committees remain.

Medicare and Medicaid do not require periodic reauthorization, but most other programs do require periodic reauthorization (normally every three years). Given the turnover rates, rarely now—in contrast to the period before 1965—does a program come up for regular renewal before a committee which contains a majority of LA's who have dealt with it before.

Legislative Areas Handled by LA's

More than 98% of the respondents indicated that they also had responsibility for legislative categories other than health, and only four of the 343 respondents indicated they worked *only* on health matters. Education was the subject area of responsibility mentioned most frequently (64%). The average number of other subject areas handled was 4.6. Some reported extremely heavy legislative responsibilities: 24 House LA's reported they handled all legislative matters in the office, and 14 others reported they handled 11 or more categories. The LA's are responsible primarily for domestic/social legislation, and only a small number of health LA's dealt with military or foreign affairs legislation (Table V).

Constituent Inquiries and Problems

Along with legislative issues, 53% of the LA's also handled constituents' inquiries and problems related to federal agencies. This additional responsibility often requires considerable time and energy, as constituent mail has reached a staggering volume—more than 40 million letters were received by members of the House and 29 million by Senators, in 1981 (2). Most communications must be read, acted upon, and answered.

An understanding of the member's constituency and its political, economic, and social patterns would be helpful in the weighing of ramifications of prospective legislation on the constituency and in dealing with constituent requests. However, less than half of the LA's came from their legislator's district or state, and about a third of the LA's to health committee members did, indicating that perhaps the latter group's legislative expertise was more valued than residence in or understanding of the constituency.

Time Spent on Health Issues Weekly

Given this wide range of legislative issues and constituent matters for which LA's have respon-

TABLE V

Legislative Areas other than Health Handled by LA's

LA's	Average other areas handled (number)	% LA's not handling military/foreign
House*	5	81
Senate*	4.1	90
House health committee members	3.2	95
Senate health committee members	4.8	90

* Members of House and Senate not on health committees.

sibility, it is not surprising to find that they spend, on the average, only 9.8 hours on health legislation weekly, presumably from a regular work week, though many LA's work considerably more than 40 hours weekly. LA's to health committee members spend more time, but it should be noted that about one fifth of them spend 5 hours or less weekly on health matters (Table VI).

LA's Working Relationship with Member

After developing and organizing pertinent information and opinions on legislative matters, the LA must get them to the legislator for decision and action.

The survey contained several questions to elucidate the working relationship between the LA and the legislator: (1) Does the LA have direct access to the legislator? (2) How many hours weekly do they spend together on health legislative matters? (3) Is the time spent sufficient? (4) How influential are the views of the LA on the legislator? (5) How is information generally given by the LA to the member—verbally or by memo, or both?

By far the larger proportion of LA's (76%) have *direct access* to the legislator on issues. The remainder go through supervisors, such as the administrative assistant (11%), who is the top-ranked individual in most offices, or other staff members. House LA's have greater direct access (82%) than do Senate LA's generally (59%), probably because the Senate staffs are so much larger, and access to the senator must be more tightly controlled. However, LA's to Senate health committee members have the highest rate of direct access (89%), probably because such LA's are given wide discretion in determining policy proposals—senators have membership on more committees than their House counterparts, and time constraints require direct access to them.

An average of about 1.5 hours weekly was spent by LA's in personal meetings with their legislators on health legislation. LA's to health committee members spent more time with their legislators: LA's to Senate health committee members spent 1.87 hours, and LA's to House health committee members spent 2.53 hours.

Is the time spent with the member sufficient? A majority of LA's (52%) indicated that they had "enough" or "plenty" of time; the remainder indicated they could use more time, or had too little.

When asked about the influence of their views on their legislators, 49% said they had "very much" or "much" influence, 33% indicated "moderate" influence, and only 18% indicated they had "some" or "little" influence. Generally, Senate LA's and Senate health committee members' LA's had higher opinions of their influence than their House counterparts.

The flow of information to and from members is largely verbal. Among all LA's, 30% reported that nearly 100% of the information given was verbal. The figures were considerably lower for LA's to Senate health committee members (12%), and also Senate LA's (14%), probably reflecting the

TABLE VI

Number of Hours Spent Weekly by LA's on Health Legislation

	Avg hours weekly	0–5 hours %	6–10 hours %	10–20 hours %	20+ hours %
House*	7.6	53	19	19	10
Senate*	11.97	24	15	50	12
House health committee members	16.35	20	0	45	35
Senate health committee members	21.5	16	0	28	56

* Members of House and Senate not on health committees.

heavier committee workload of senators, and therefore the need for more extensive briefing by written memos.

Future Career Plans

Future career plans of individuals can reveal the level of interest in aspects of their present work. The LA's were asked about (1) their own probable future careers, and (2) what kind of work their immediate predecessors are now doing.

Only 3% of respondents indicated they would be working in the health field in the future. Most intend to work outside government, many in association lobbying work, law, or business. Nearly one third, however, indicated that they intend to make congressional staff work a career (Table VII).

TABLE VII
LA's Future Career Work Plans

Future career choice	%
Congressional staff	29
Association lobbying	23
Law	16
Business	15
Political career	5
Health medicine	3
Other	9

Their immediate predecessors have shown a similar disinclination to health matters. *Only 2%* have continued in health legislation work in other congressional offices, over one third have left the Washington area, a fifth have remained in the same office in different work (promoted), and a tenth are in other congressional offices, doing different kinds of work. Of the remaining third who have stayed in Washington, most have become lobbyists or "consultants." Many others went to federal agencies (presumably to staff the new Republican administration), and others moved to political campaigning, media work, teaching, and other fields.

Route of Entry

The routes by which LA's came to their present positions are diverse. Twenty per cent began as congressional interns, working for little or no pay in congressional offices as an educational experience, generally through college credit programs. Ten per cent began as campaign volunteers. A large group came by way of a "network," such as a personal acquaintance, being a member of a family well-known to the member, or through friends having knowledge of a job opening. Others indicated they were former lobbyists or had worked in politics or at legislative and administrative posts at the state or local levels. A large number indicated they had come to their posts through lower-paying congressional office jobs, such as caseworker, receptionist, or district office caseworker. Several indicated unusual entry routes—as one LA put it, "Sang 'God Bless America' at congressman's testimonial dinner!" Several were recommended to the member by former professors. The largest category indicated that they had simply "applied"—mostly through the Congressional Placement Office (Table VIII). Of the 31 persons who indicated that they came from campaigns, 17 were women and 14 were men. Of those who listed entry through lower-paid jobs, such as caseworker, 35 were women and six were men.

Discussion

The data presented would seem to lead to a dismaying conclusion for those individuals and groups concerned with health policy, which is that the characteristics and work patterns of LA's present a formidable hurdle to the shaping of appropriate policy, and to the opportunity for such groups to make their views known.

The data show that LA's are young and generally without considerable scientific, health pro-

TABLE VIII
Route of Entry into First Congressional Job (%)

Entry Route	Overall %	House* %	Senate* %	House health committee member %	Senate health committee member %
Congressional intern	20	20	25	16	11
Campaign	10	6	30	11	11
Network	20	21	15	21	15
Lower-level post	14	16	8	5	7
Applied	26	25	18	26	40
Other	12	12	5	21	15

* Members of House and Senate not on health committees.

fessional, or health administration education or experience. They have a very high turnover rate, which precludes the accumulation of experience on the job, and have had limited prior experience in congressional legislation generally and health legislation specifically. They have little expectation of career work in the health field. They labor under a heavy and stressful work load, which includes required attention to at least four other subject areas and to constituent services, and have little time in direct meetings with their legislators on health matters.

What the data do not, and could not, show are other characteristics discerned by seasoned observers of Congress. The LA's are generally a very hardworking, ambitious, and often politically astute group, nearly always open to the properly presented views of individuals or of interest groups. LA's are acutely aware of their legislator's concerns about the interests of the constituency, and thus are very willing to hear from and meet with prominent constituents. They are generally conscientious in presenting the views they have heard to their legislators.

Also, as noted earlier, the committee system itself assures that legislation and policy are handled carefully and at length, and interested individuals and groups have full opportunity to make their views known there. Additionally, LA's often bring their legislators' views to professional committee staff for discussion.

Summary

The study points quite clearly to the need for the medicine and health community to develop a process by which it can assist a hard-pressed, intelligent, and influential staff group in the Congress to obtain information about biomedical research and health care issues. Also, it is clear that such information must be presented systematically, in succinct, pithy, and intelligent lay terms, in a continuous, long-term fashion.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Gastric Polyps*

RICHARD H. MARSHAK, M.D., ARTHUR E. LINDNER, M.D., AND DANIEL MAKLANSKY, M.D.

Unlike polyps in the colon, gastric polyps are uncommon lesions. Usually they do not cause symptoms and are discovered in the course of routine studies or during investigations for other complaints. Gastric polyps are associated with hypochlorhydria or achlorhydria, chronic gastritis, and gastric carcinoma. It is the concern that these polyps may be premalignant that attracts most interest and also directs management. Recent careful reviews of the histology of gastric polyps have provided reassuring data about the general low incidence of carcinomatous change and have also helped to identify those polyps that do bear a malignant potential.

The overall incidence of gastric polyps in autopsy series is approximately 0.4%. Tomasulo (1) quotes one series with 50 cases in 7,000 autopsies and another with only 17 cases in 11,000 autopsies. Although most polyps are asymptomatic, they may become ulcerated and bleed or, rarely, they may prolapse into the duodenum and cause gastric outlet obstruction.

Since the adenoma-carcinoma sequence (2) has been the subject of much discussion with respect to colon cancer, it is appropriate that the risk of malignant change in gastric polyps should also be of concern. More than half a century ago, Stewart (3) reported that there was an associated carcinoma in 28% of patients with gastric polyps and that in 5% of patients with gastric carcinoma there were associated polyps. Over the years investigators have reported an incidence of malignant change in gastric polyps ranging from 0 to 51% (1). It now appears that much of this variability reflects differences in the histologic classification of polyps. Only adenomatous polyps, which by modern criteria are uncommon gastric lesions, are premalignant. The much more common hyperplastic polyps have a very low malignant potential, or none at all. Failure to distinguish these two types of polyps has tended to mask the relationship of adenomas to cancer. When all gastric polyps are considered, the risk of malignancy is very low, and the associated carcinoma that may occur usually arises in nonpolyp epithelium, perhaps because both polyps and carcinoma tend to arise in a setting of chronic gastritis.

Classification of Gastric Polyps

Four types of gastric polyps have been identified (1, 4, 6–8).

1. *Hyperplastic or regenerative polyps* are the most common, comprising 75% to 90% of gastric polyps. These polyps, which may be single or multiple, are usually small in size (less than 1.5 cm), sessile or pedunculated, smooth in contour, and shaped like a dome. They may occur anywhere in the stomach. On histologic examination, there is a single layer of surface epithelium. Most of the polyp consists of hyperplastic, elongated gastric glands with abundant, edematous stroma. Hyperplastic polyps are not true neoplasms. They appear to represent an inflammatory response of the gastric epithelium and once observed they grow slowly in size or not at all. Malignant change has rarely been reported in hyperplastic polyps.

2. *Adenomatous polyps* make up almost all other gastric polyps. These are soft lesions, true neoplasms, which tend to be located as single polyps in the antrum. The surface may be flat or irregular, with papillary and villous projections. Histologically, gastric adenomas resemble adenomatous polyps of the colon. They are composed of cells with hyperchromatic, elongated nuclei arranged in a picket-fence pattern (1). Papillary and villous patterns are seen and gastric glands are uncommon. Adenomas are expanding, rather than stable, lesions. Malignant change in adenomas is not uncommon and in some reports ap-

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* From the forthcoming text *Radiology of the Stomach* to be published by W. B. Saunders Company.

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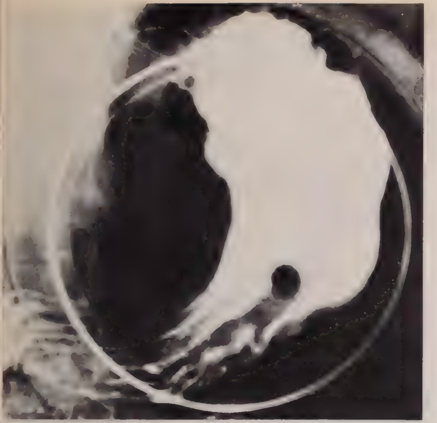

FIG. 1. Hyperplastic Polyp. There is a 1 cm sharply demarcated filling defect in the middle third of the stomach. The rugal folds are thin on the greater curvature aspect of the stomach.

proaches 40% (4). Coexisting carcinoma of the stomach occurs two to three times more often than in stomachs containing hyperplastic polyps. The gastric polyps that may occur in patients with familial polyposis are frequently tiny and difficult to identify. They may be either hyperplastic or adenomatous.

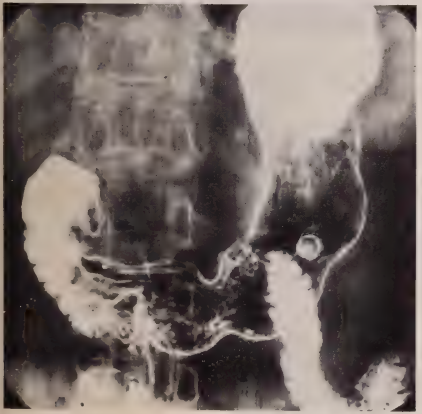

FIG. 2. Hyperplastic Polyp. A single small circular hyperplastic polyp is noted in the upper middle third of the stomach. This air contrast film was taken twenty years ago. The polyp remained unchanged for eighteen years. Two years ago the patient agreed to gastroscopy with biopsy which revealed the presence of a hyperplastic polyp associated with gastric atrophy.

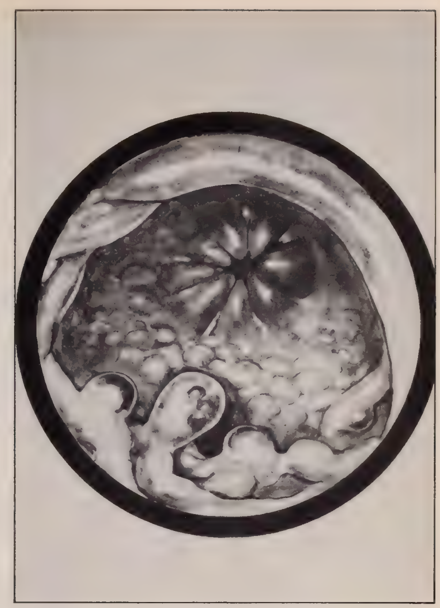

FIG. 3. Artist's rendering of gastroscopic view. Gastroscopy reveals multiple small hyperplastic polyps in the antrum of the stomach, associated with superficial erosions. The erosions are too superficial to be seen on x-ray.

3. Hamartomatous polyps are composed of densely packed gastric glands characteristic of the portion of the stomach in which they occur. Most are small, less than 2 cm in size. These are the gastric polyps that are seen in the Peutz-Jeghers syndrome. Their relationship to carcinoma is uncertain. Hamartomatous polyps are rare gastric lesions.

4. Retention polyps are smooth, edematous polyps that occur rarely in the stomach. They are composed of dilated cystic glands and stroma. These are the gastric polyps seen in patients with Cronkhite-Canada syndrome (5).

5. Villous tumors are intraluminal, trabeculated, and slightly irregular. They vary in size, are usually sessile but sometimes pedunculated, and on occasion produce a contour defect. They have a malignant potential, just as they do in the colon. These lesions are soft, sometimes multiple, presenting as a cluster of raspberrylike filling defects on roentgen examination. When ulceration, fixation, or rigidity of the wall is seen, a superimposed carcinoma should be suspected.

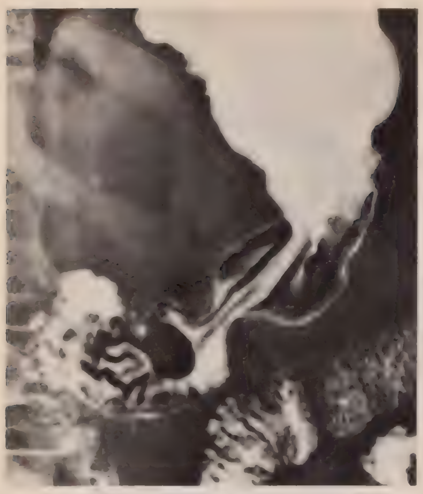

FIG. 4. Large Hyperplastic Polyp. There is a large, smooth, circular defect in the antrum of the stomach measuring 2 cm in diameter. The adjacent rugal folds are thin. There are no ulcerations.

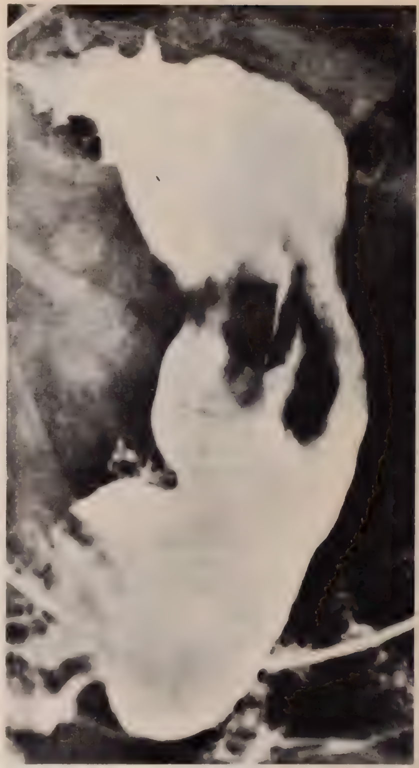

FIG. 5. Hyperplastic Polyps. There are two spindle-shaped polypoid defects in the middle third of the stomach, each measuring almost 5 cm in length. During a period of observation of eight years, those polyps have remained unchanged in size and configuration. Biopsy revealed hyperplastic polyps.

Management of Gastric Polyps

Polyps which are bleeding or causing obstruction can be removed either by surgical excision at laparotomy or by snare polypectomy at gastroscopy (9). Whether asymptomatic polyps should be removed is a decision based upon the risk of carcinoma. Since this risk depends so much on the type of polyp involved, one method of management is to obtain gastroscopic biopsy. Although such biopsy is too limited to exclude cancer elsewhere in the lesion, it should provide histological data to distinguish an adenomatous from a hyperplastic polyp. Adenomatous polyps warrant excision because they carry a malignant potential. Current data suggest that asymptomatic gastric polyps less than 2 cm in diameter with roentgen and biopsy features of hyperplastic polyps can be observed.

Roentgen Features

A polyp appears as a filling defect which interrupts or displaces the adjacent normal rugal folds (10). These folds may become shallow as they approach the polyp or be displaced around it. The gastric wall surrounding a polyp is pliable. The adjacent mucosa is often atrophied but on occasion there is hyperruggosity.

Hyperplastic polyps are usually smooth, circular, and less than 1 cm in diameter (Figs. 1, 2). They may be single or multiple (Figs. 3–9). Occasionally hyperplastic polyps are large (Figs. 4, 5), measuring 6-7 cm in diameter. Despite the large size of these polyps the contours remain smooth. Ulcerations which may occur are too superficial to recognize on roentgen study. Contour defects are not seen. Pedicles may or may not be present. These polyps can be seen in any part of the stomach. Antral polyps may prolapse into the duodenal bulb.

Adenomatous polyps may be smaller than hyperplastic polyps. More often they are larger in size, usually over 1.5 cm in diameter, sessile, ir-

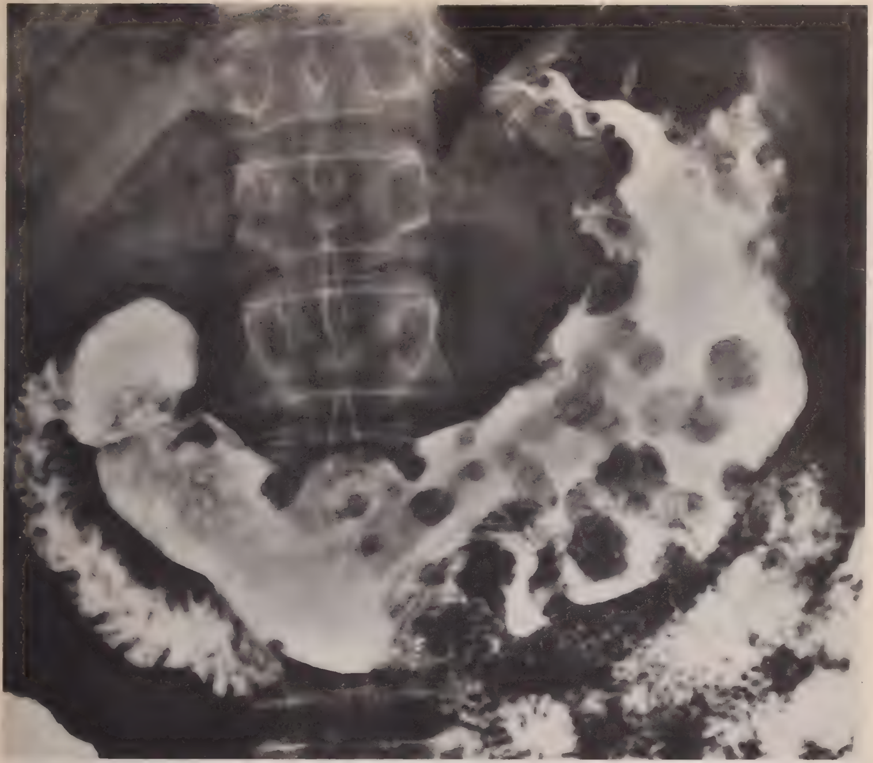

FIG. 6A. Multiple Polyps. There are multiple smooth filling defects varying in size from 1 to 2.5 cm in diameter distributed throughout the stomach. No discrete ulcerations are identified. Multiple polyps of this type are usually hyperplastic. In our experience multiple adenomatous polyps are uncommon.

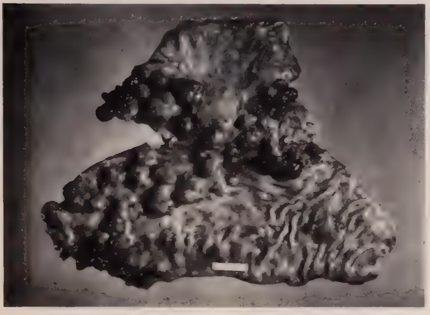

FIG. 6B. Same case as 6A. Surgical specimen revealing the discrete multiple polyps distributed throughout most of the stomach. The adjacent rugal folds are thin in contradistinction to lymphosarcoma where the rugal folds are frequently enlarged.

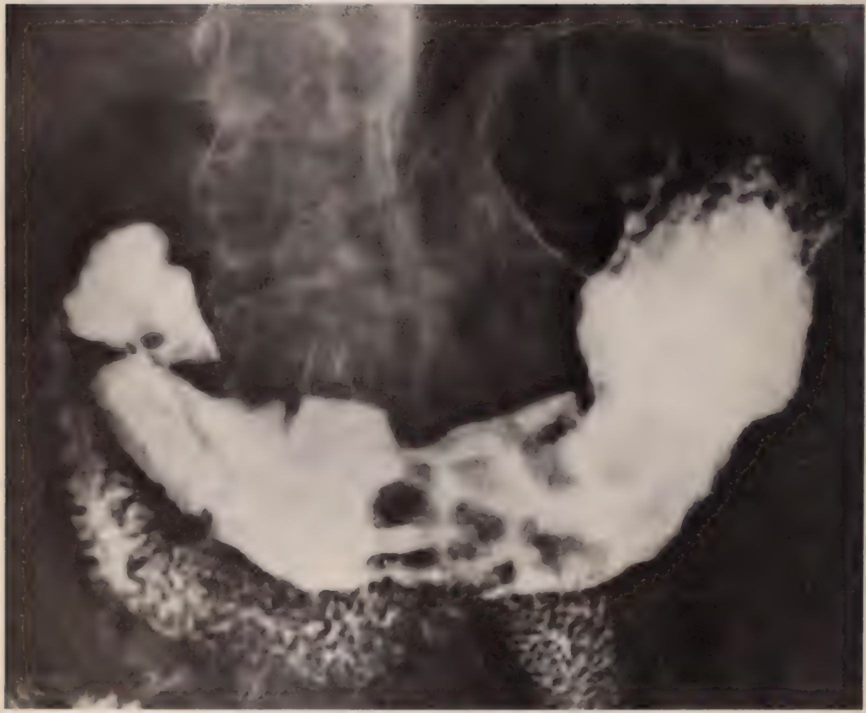

FIG. 7 Multiple Polyps. Multiple, discrete, circular defects are identified in the middle third of the stomach, ranging from 0.5 to 1.5 cm in diameter. Gastroscopy and biopsy of several polyps revealed hyperplastic polyps.

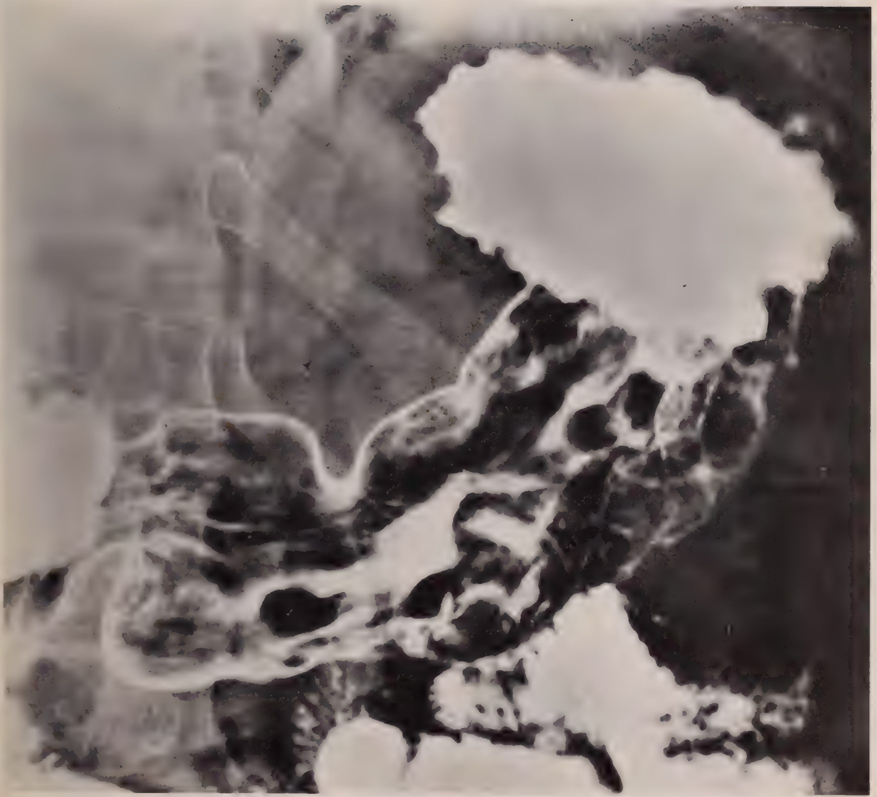

FIG. 8. Multiple Polyps. Multiple small, circular, hyperplastic polyps are identified on the posterior wall of the stomach in air contrast examination. Follow-up studies over a period of eight years revealed no change.

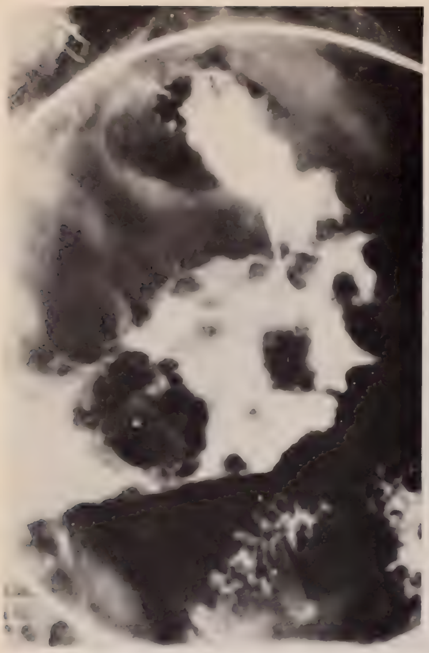

FIG. 9. Multiple polyps of the stomach. Small, moderate, and large polyps are seen throughout the stomach. These remained unchanged for a period of fifteen years, at which time the patient underwent surgery for a carcinoma of the colon. The patient expired several months after surgery. Autopsy revealed multiple hyperplastic polyps.

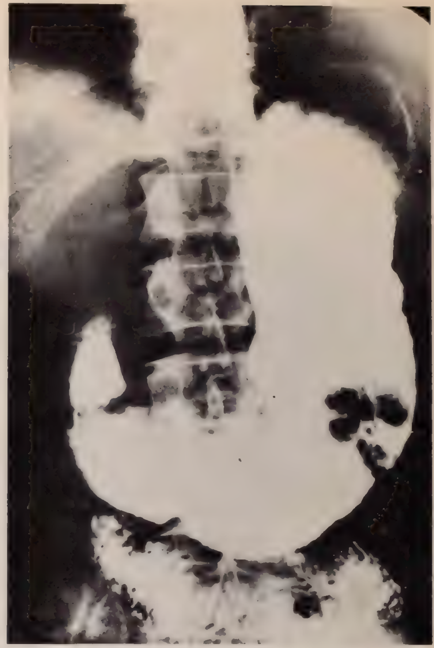

FIG. 10. Adenomatous polyp. There is a mushroomlike polyp on the greater curvature aspect of the proximal portion of the antrum of the stomach, associated with a short, thick pedicle. Removal revealed an adenomatous polyp.

regular, elliptical, or mushroom-shaped (Fig. 10). They may be single or multiple. Adenomatous polyps are relatively infrequent when compared to hyperplastic polyps. The presence of both types of polyps in a single stomach is rare.

Multiple Polyps. Hyperplastic polyps may be multiple, and when this occurs they may be uniform in size or vary considerably from small lesions less than 1 cm in diameter to large, bulky masses. They usually retain their smooth contour but may be irregular when they are large. The malignant potential of hyperplastic polyps is nil, even when the polyps are multiple and large.

Adenomatous polyps are usually single, but on occasion may be multiple (Fig. 11). Because there is risk of malignancy in adenomatous polyps, differentiation of hyperplastic polyps is important (Fig. 12). One must always be alert to the possible coexistence of carcinoma with either hyperplastic or adenomatous polyps.

Differential Diagnosis

Menetrier's disease, Canada-Cronkhite syndrome, and hyperrugosity are easily differentiated from multiple polyposis.

There are a variety of lesions of the stomach which may produce smooth filling defects of varying size. These include eosinophilic granuloma, submucosal tumors such as myomas and neurofibromas, aberrant pancreatic tissue, adenomyomas (Fig. 13), myoepithelial hamartomas, gastric cysts and duplications, enlarged folds seen on end (Fig. 14), lymphangiomas, inflammatory fibroid polyps, and on rare occasions, tiny lymphomas and carcinomas.

Differentiation of these lesions from one another and from gastric polyps is obviously difficult when they are small (11). Certain rules, however, can be followed. A polyp rarely shows ulceration deep enough to be seen on an x-ray. This lack of ulceration will frequently be sufficient to differ-

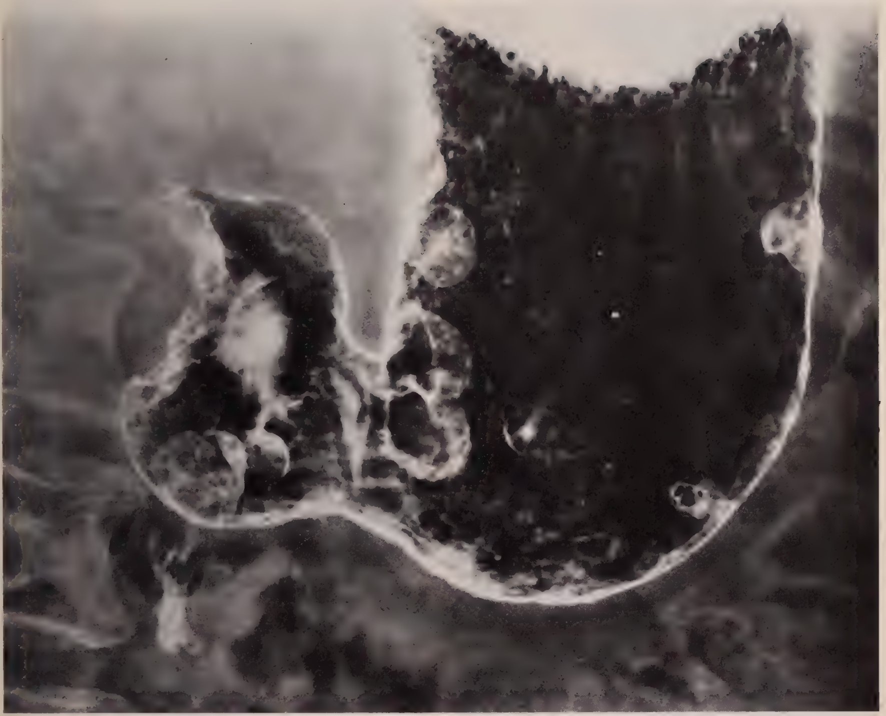

FIG. 11. Multiple polyps of the stomach and a carcinoma. Air contrast study reveals the presence of multiple elliptical and circular polyps involving the distal two-thirds of the stomach ranging in size from 1 to 3 cm in diameter. There is also a carcinoma of the antrum.

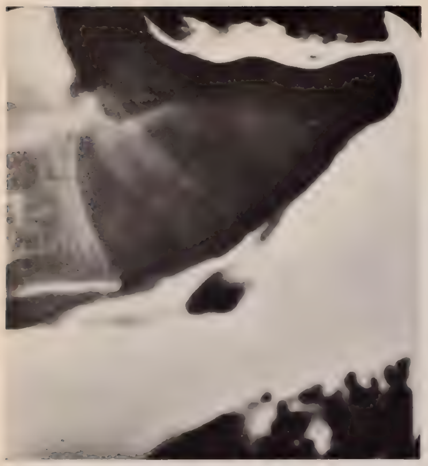

FIG. 12. Carcinoma associated with an adenomatous polyp. There is an elliptical defect on the lesser curvature aspect of the antrum of the stomach measuring 1.5 cm in greatest diameter. Gastroscopic removal of this lesion revealed an adenomatous polyp with malignant changes. In our experience, carcinomatous change in an adenomatous polyp less than 1.5 cm in diameter is uncommon.

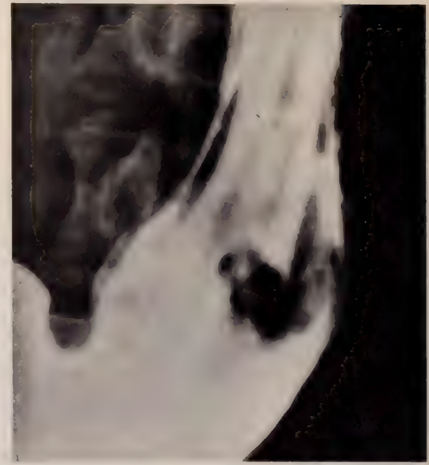

FIG. 14. Gastric folds seen on end simulating a polypoid lesion. Multiple compression spot films revealed the true nature of the lesion, which was confirmed at gastroscopy.

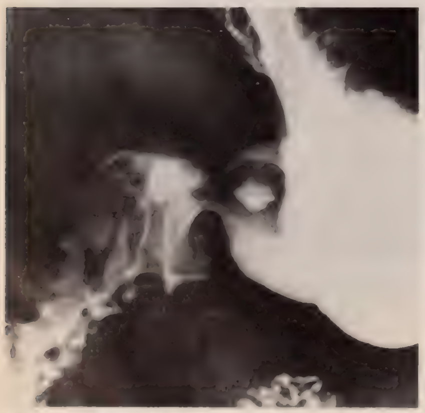

FIG. 13. Adenomyoma of the stomach. There is a circular filling defect of the antrum with a central barium-filled depression. A single roentgen diagnosis is impossible in this case.

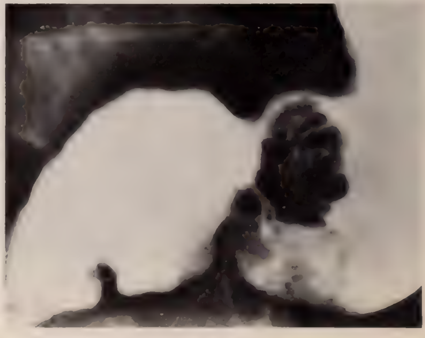

FIG 15. Villous tumor of the stomach. There is a 3 cm lobulated defect involving the middle third of the stomach. The lesion is trabeculated, with the lacelike pattern typical of villous tumor. The lesion was easily compressed, fluoroscopically.

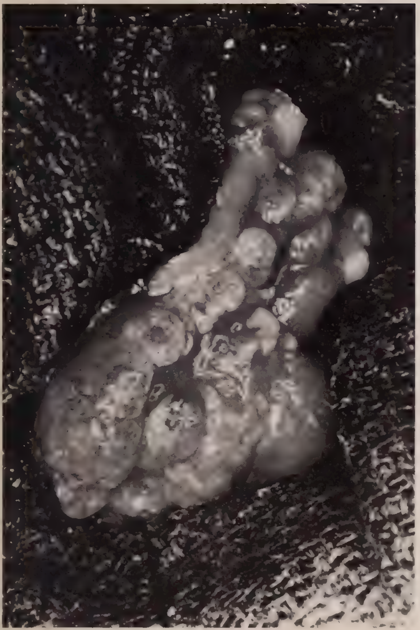

FIG. 16. Surgical specimen of Fig. 15: villous tumor. There is a lobulated polypoid mass measuring 3 cm in diameter with multiple fronds extending from the main portion of the mass.

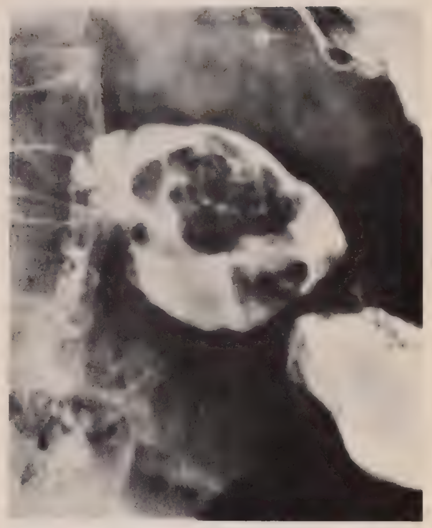

FIG. 17. Villous tumor of the stomach prolapsing into the duodenum. This pedunculated villous tumor originated in the antrum of the stomach. During fluoroscopy this lesion was seen to prolapse through the pylorus.

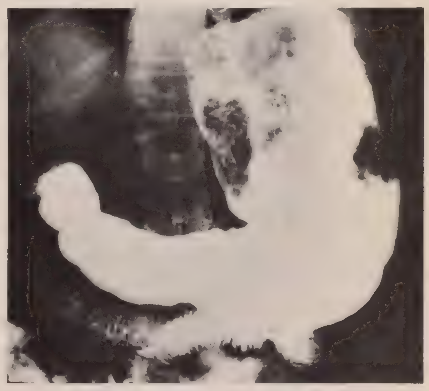

FIG. 18. Giant villous tumors of the stomach. There is a very large tumor occupying the proximal half of the stomach. The lobulated surface and the lacelike pattern is typical of a villous tumor.

entiate a submucosal tumor, an adenomyoma, or a pancreatic rest in which the duct fills with barium at the center of the lesion. A benign peptic ulcer may be surrounded by a zone of edema that simulates a polypoid lesion. Metastatic tumors to the stomach can present as polypoid lesions, but they are larger, frequently ulcerated with an irregular contour. It is rare for a polypoid carcinoma to present as a smooth, small defect. Small submucosal tumors, when not ulcerated, can simulate a polyp. More often submucosal tumors are larger and often ulcerated.

Villous tumors, when small, are impossible to differentiate from other small polypoid lesions (Figs. 15, 16). When larger they have the characteristic configuration described above (Figs. 17, 18).

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Submitted for publication July 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Overwhelming Mycobacteriosis in an Immunodeficient Homosexual

JENNY S. WAXMAN, M.D., ANTONIO SUBIETAS, M.D., MOISES MALOWANY, M.D., AND MARK L. TAFF, M.D.

Abstract

We present the case of a young homosexual man with T-cell deficiency who developed a disseminated mycobacteriosis involving multiple organs. The problems of immunosuppression and multiple infections in homosexual men are discussed.

Wide attention has been focused recently on immunosuppression in homosexual men who developed various opportunistic infections and neoplasms (1–5). This report describing an immunosuppressed patient with disseminated mycobacteriosis adds to this subject.

Case Report

A 29-year-old man was hospitalized because of spiking fever of seven weeks' duration, diarrhea, vomiting, and weight loss for the last fortnight. His history included two episodes of hepatitis, eleven and three years previously; surgery for pilonidal sinus fifteen years ago; and epididymitis one year ago. He confessed to homosexuality for many years and to frequent amyl nitrite abuse. Skin lesions diagnosed as psoriasis appeared about one year ago, and were treated with topical steroid medication. Dyspnea with nonproductive cough started about three months prior to this admission.

He appeared well nourished, alert, with fever of 40°C (104°F) and occasional bouts of dry cough. His tongue was dark, and large scaly plaquelike lesions were present over the elbows, gluteal folds, and tibial areas, with smaller indurations over the soles. Crepitant rales were heard over the apices of both lungs. The liver was palpable 5 cm below the right costal margin, but there was no splenomegaly or lymphadenopathy. Physical examination was otherwise unremarkable.

He was anemic with hemoglobin of 9.6gr% and hematocrit of 20%. His white-cell count was 4200/ml, with 77% neutrophils, 2% bands, 9% lymphocytes, 5% monocytes, 6% eosinophils, and 1% metamyelocytes. Complement fixing antibodies showed a fourfold increase in cytomegalovirus (CMV) titer and a twofold increase in herpes simplex virus (HSV) titer. Serum levels of IgG and IgM were normal. IgA was elevated to 700 mg%. Immunologic studies were performed on two occasions at the New York University Medical Center and showed lymphopenia of less than 600 per microliter and reversal of T(helper)/T(suppressor) ratio. In mixed lymphocyte culture, decreased stimulation of lymphocytes to mitogens (phytohemagglutinin, concanavallin A, and pokeweed) as well as to antigens (diphtheria, tetanus, candida, SKSD, and PPD) was also observed. A more detailed discussion of the patient's immunologic status will appear elsewhere (6).

Scrapings of the patient's tongue revealed *Candida albicans.* Endoscopy of the upper and lower gastrointestinal tracts for possible visceral Kaposi's sarcoma proved negative. Biopsy of the rectal mucosa revealed only nonspecific chronic inflammatory changes. A stool assay for *Clostridium difficile* toxin was negative. Chest x-rays showed increased interstitial markings bilaterally. C-T scan of the chest and abdomen was reported as negative. The biopsy of the scaly skin lesion of the elbow showed psoriasiform dermatitis. The bone-marrow biopsy, done twice, revealed nonnecrotizing granulomas composed of

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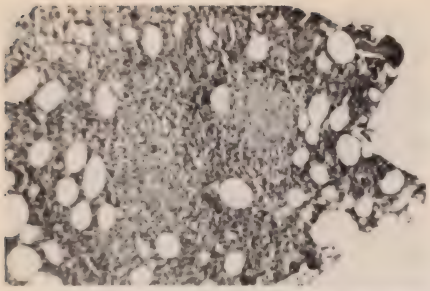

FIG. 1. Bone marrow showing two discrete epithelioid cell granulomas (center) (×100).

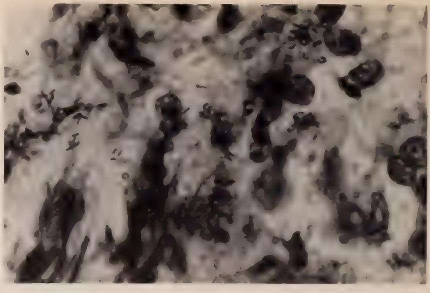

FIG. 2. AFB in the bone marrow (×1000).

large epithelioid histiocytes with abundant pale pink and vacuolated cytoplasm and round or oval nuclei. The histiocytes were arranged concentrically and were surrounded by a few lymphocytes. Giant cells were not seen. Numerous acid-fast bacilli (AFB) were seen throughout the bone marrow (Figs. 1, 2). Subsequent biopsy of a right supraclavicular lymph node showed a complete effacement of the normal nodal architecture. No lymphoid follicles with germinal centers were identified; instead, there was a diffuse cellular proliferation with multiple and prominent plasma cells and histiocytes. The lymph node disclosed no granulomas, but the AFB stain did show multiple bacilli (Figs. 3, 4), despite previous intensive treatment with INH, Rifampin, Vancomycin, Ethambutol, Sulfa-Trimethoprin, and Cefadyl. Cultures of the sputum, gastric fluid aspirate, and bone marrow yielded a slow growing nonpigmented acid-fast bacillus at 25°C and 37°C in a 5-percent CO_2 atmosphere. Based on cultural and biochemical characteristics (Table 1), the organism was identified as *Mycobacterium avium* intracellulare complex (MAIC).

The diagnosis was confirmed by the laboratories of the New York City Department of Health and the Centers of Disease Control.

The treatment resulted in a general gradual improvement of the patient's condition. At the time of this writing he is being followed in the outpatient clinic and is being treated with the transfer factor and an experimental drug, Ansamycin (LM-427).

Discussion

This patient's history is indicative of his multiple infections over the previous eleven years. The laboratory data includes evidence of CMV and HSV infections as well as IgG hepatitis A antibody and hepatitis B core antigen, the latter indicating a carrier state of the hepatitis B. The high level of serum IgA in our patient could reflect hyperreactivity of the gut-related lymphoid tissue, as previously postulated (4). Lymphopenia, the salient feature observed in reported male homosexuals (1–4), has also been found in our pa-

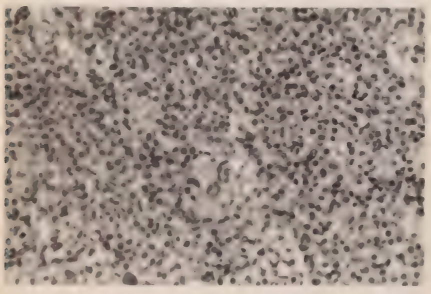

FIG. 3. Lymph node with a picture of "non-specific lymphadenitis" showing multiple plasma cells and histiocytes (×157).

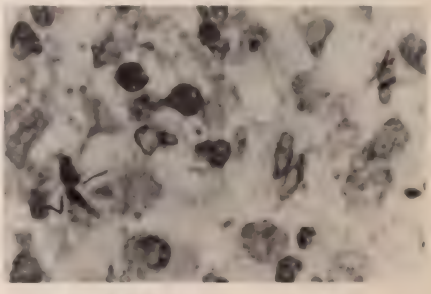

FIG. 4. AFB in the lymph node (×1000).

TABLE 1
Microbiologic Characteristics of Mycobacterium avium Intracellulare Complex

Growth at 25°C	+	Urease	–
Growth at 37°C	+	Arylsulfatase	–
Pigment	–	Growth on 5% Na Cl	–
Rate of growth	10-21 days	Iron uptake	–
Niacin	–	Resistance to T2 H	+
Nitrate reduction	–	Tellurite reduction	+ in 3 days
Catalase activity	+	Tween 80 hydrolysis	– in 10 days

tient. Analysis of his cellular immune system showed a reversal of T (helper)/T(suppressor) ratio and decreased response to mitogens and antigens, indicative of marked deficiency of his cellular immunity.

Siegal and associates (4) considered the CMV infection a "candidate initiator" of the immune defects that may further predispose to other opportunistic infections such as pneumocystosis, candidiasis, aspergillosis, cryptococcosis (7–9), and, in our case, mycobacteriosis. The MAIC is considered to be of relatively low virulence, and in some geographic areas it is detected incidentally as an occult asymptomatic invader (10–12). Venereal transmission of CMV appears to be highly prevalent in the male homosexual population; in a recent report 179 out of 190 (94%) showed evidence of this infection (7).

CMV, steroids (3, 4), and use of "recreational" drugs (7, 13) have all been implicated in the process of acquired immunodeficiency in homosexual men, and all of them were operational in our patient. Their individual importance, however, singly or in combination, has yet to be established and proved.

Acknowledgments

The authors thank Dr. Peter Nicholas and Dr. Sharon Lewin for providing the clinical data on the patient.

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Submitted for publication May 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Modulation of Presynaptic Neurotransmission

I: Theories of the Mechanism of Synaptic Vesicle Fusion with the Presynaptic Axonal Plasma Membrane

NATHAN MOSKOWITZ, Ph.D., AND SAUL PUSZKIN, Ph.D.

Abstract

An integrated theory of presynaptic chemical neurotransmission is presented. It is postulated that calcium induces synaptic vesicle exocytosis by activating axon terminal actomyosin, synaptic membrane phospholipase A_2, adenylate cyclase, calcium/calmodulin- and cAMP-dependent protein kinases. The release of arachidonic acid by phospholipase A_2 activation and subsequent generation of prostaglandins by synaptic vesicle prostaglandin synthetase may continually modulate neurotransmitter release. The concerted action of many enzymatic and non-enzymatic events in the presynaptic axon terminal may explain how neurotransmitter release is finely regulated.

Introduction

The most accepted model explaining the sequence of events occurring in chemical neurotransmission is the vesicle hypothesis. This hypothesis was formulated after the discovery of neurotransmitter-containing vesicles in axon terminals (1, 2) and the observation that neurotransmitter release is quantal in nature (3). In essence, the hypothesis states that upon depolarization of the presynaptic plasma membrane, Ca^{2+} enters the axon terminal and leads to apposition and fusion of the synaptic vesicle with the presynaptic membrane. Consequently, quantal packets of neurotransmitter are released from the synaptic vesicle into the synaptic cleft, then interact with the postsynaptic membrane and induce an endplate potential. Although this model has been criticized (4), biochemical (5), physiological (6), morphological (7), and immunological (8) studies tend to confirm it.

The theories presented in this paper enlarge upon the vesicle hypothesis and address the mechanisms involved in the modulation of Ca^{2+}-mediated synaptic vesicle apposition and fusion with the presynaptic membrane. The theories are based primarily on our recent findings and are correlated with the findings of others. It is suggested that Ca^{2+} interacts with multiple enzymes as well as nucleotide, protein, and lipid messengers to initiate and modulate neurotransmission.

Brain Contractile Microfilaments

Electron microscopy of axon terminals reveals that synaptic vesicles are located at least 50 Å from the presynaptic membrane (9). In earlier studies, Berl et al. postulated that Ca^{2+} may initiate exocytosis by activating brain myosin ATPase located on synaptic vesicles (10), thereby allowing plasma membrane actin to interact with myosin (11), leading to contraction and hence movement of the synaptic vesicle to the plasma membrane. Another Ca^{2+}-dependent mechanism of actomyosin contraction is myosin phosphorylation mediated by myosin light chain kinase (12, 13).

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This paper derives from Dr. Moskowitz' studies in the combined M.D./Ph.D. program, with Dr. Puszkin as thesis advisor.

This study was supported in part by NIH grants Number NS 12467 and Number HL27928 to S.P.

Recently it has been demonstrated that myosin light chain kinase activity is dependent not only on Ca^{2+} but also on calmodulin (13). Calmodulin is a highly conserved, ubiquitous, acidic protein with a molecular weight (M_r) of approximately 17,000 (14). In the absence of Ca^{2+}, calmodulin exists in a nonactive conformation. Upon Ca^{2+} binding to the molecule, calmodulin's conformation is altered, allowing it to bind to and activate a variety of enzymes. It is possible, therefore, that calmodulin, which is present in brain and found in synaptic vesicles (15), may facilitate exocytosis by activating myosin light chain kinase.

Actomyosin contraction may mediate the propulsion and movement of synaptic vesicles, but can it also mediate the fusion of two distinct membranes? The mixture of molecules between two adjacent stable bilayers is energetically unfavorable and can take place only if destabilization of membranes occurs (16). To date no evidence has been presented that actomyosin contraction is capable of producing bilayer mixing.

Calcium as Fusogen

It has been hypothesized that Ca^{2+} ions may directly induce fusion of membranes via neutralization of membranal surface charges (17) or induction of membrane phase transitions (16). These hypotheses, however, are based on work with synthetic phospholipid vesicles. Work dealing with synaptosomes, a more physiologically relevant model, indicates that Ca^{2+} by itself cannot induce neurotransmitter release from synaptosomes (15); therefore, mechanisms other than the direct action of Ca^{2+} must be involved in mediating fusion.

Synaptic Vesicle Phospholipase A_2, Prostaglandin Synthetase, and Protein Kinase Activity

Phospholipase A_2 (PLA_2) is an enzyme that hydrolyzes the fatty ester linkage of sn-phosphoglycerides in the 2 position. Recently we found that brain synaptic vesicles have endogenous PLA_2 activity (18). The enzyme is Ca^{2+} dependent, has a pH optimum of 9.0, an apparent K_m of 60 μM, and a relative V_{max} of 2 nmol/mg/hr. Furthermore, calmodulin increased the enzyme's V_{max} approximately fivefold (Table 1). Hydrolysis of phosphatidylcholine by PLA_2 leads to the formation of lysolecithin and free fatty acid. Lysolecithin induces membrane fusion (19, 20) and is implicated in the secretion of chromaffin granules (21). It is possible, therefore, that Ca^{2+}/calmodulin stimulation of synaptic vesicle PLA_2 may be a mechanism whereby synaptic vesicles fuse with the presynaptic membrane. This hypothesis is supported by the demonstration that exogenous PLA_2 induces depletion of synaptic vesicles from peripheral and central axon terminals (22).

Phospholipase A_2 hydrolysis of phosphoglycerides may release arachidonic acid, the precursor of prostaglandins, which are ubiquitous cellular modulators (23). We observed, using [^{14}C]-β-arachidonic acid phosphatidylcholine as substrate, that synaptic vesicle PLA_2 releases arachidonic acid (18). In order to determine the metabolic fate of arachidonic acid, we incubated synaptic vesicles with [^{14}C]-arachidonic acid (specific activity 55.8 mCi/mmol) for 20 minutes as described previously (24). The reaction was stopped, and vesicles were extracted, processed and layered on Silica G chromatographic plates (25). Thin-layer chromatography was performed using chloroform:methanol:acetic acid:water (90:8:1:0.8). The radiochromatogram scan obtained using a Packard radiochromatogram scanner is illustrated in Figure 1. The peaks shown cochromatographed with prostaglandins E_2, $F_{2\alpha}$, A_2, and B_2 standards. Definitive identification of these compounds awaits further analysis by gas chromatography-mass spectrometry. Our preliminary results made it appear that most of the arachidonic acid was converted to prostaglandins, indicating that synaptic vesicles may have active prostaglandin synthetase activity. Prostaglandin synthetase is commonly located in smooth endoplasmic reticulum (23). The endoplasmic reticulum origin of synaptic vesicles (24, 26) may explain their capacity for prostaglandin synthesis. It has been reported that synaptic vesicles store but do not synthesize prostaglandins (27). Those results, however, were based on the use of linoleic acid rather than arachidonic acid as substrate.

The proposed metabolic pathway of arachidonic acid in brain synaptic vesicles is outlined in Figure 2. Arachidonic acid is oxygenated by prostaglandin synthetase to PGG_2, a 15-hydroperoxy prostaglandin endoperoxide, and then reduced by the same enzyme to PGH_2, 15-hydroxy prostaglandin endoperoxide. The highly unstable PGH_2 is converted to $PGF_{2\alpha}$ or PGE_2 by endoperoxide reductase or prostaglandin E isomerase, respectively. Prostaglandin E_2 may be converted to PGA_2 or PGB_2 by dehydrogenases. However, this is not certain, since these metabolites are converted from PGE_2 by non-enzymatic means as well (28, 29). PGE_2 has been demonstrated to be synthesized in the brain (30), to inhibit neurotransmission (30), and to act as a sedative (31). Also, $PGF_{2\alpha}$ is synthesized in the brain and gen-

TABLE I

Effector of Synaptic Vesicle PLA_2 V_{max}

Effectors (concentration)	Relative V_{max} nmol/mg/hr	% change/stimulation (+), inhibition (−)
Calmodulin (1 μM)	9.0	350 (+)
PGE_2 (4.0 nmol)	0.6	70 (−)
PGE_2 (4.0 nmol) + calmodulin (1 μM)	1.0	50 (−)
$PGF_{2\alpha}$ (4.0 nmol)	16.0	700 (+)
cAMP (1 mM)	3.0	50 (+)
cAMP (1 mM) + ATP (1 mM)	6.0	200 (+)

V_{max} was determined from Lineweaver-Burk transformations of substrate concentration curves (r = 0.97−0.99). Synaptic vesicles (100 μg) were incubated for 60 minutes at 37°C in the presence of 1-2 mM $CaCl_2$ with ^{14}C-β-arachidonylphosphatidylcholine (0.2−4.0 nmol).

erally stimulates neurotransmission (30). The mechanisms of these prostaglandin actions remain obscure. It is speculated that PGE_2 and $PGF_{2\alpha}$ may exert their effects via stimulation of adenylate and guanylate cyclases, respectively (32, 33).

The hypothesis that PGE_2 and $PGF_{2\alpha}$ exert their neuroregulatory actions by modulating presynaptic membranal PLA_2 was examined. Synaptic vesicles were incubated with nanomolar concentrations of these compounds and with increasing concentrations of radio-labeled phosphatidylcholine as described previously (18). The substrate concentration curves were analyzed by Lineweaver-Burk plots and their kinetic parameters determined (Table I); $PGF_{2\alpha}$ increased the V_{max} by 700%; moreover, PGE_2 inhibited the V_{max} by 70% as well as reversing the calmodulin potentiation of PLA_2 activity (Table I). Thus it appeared that the stimulation of a single enzyme, PLA_2, could lead to the production of one product, lysolecithin, which may initiate exocytosis, and another product, arachidonic acid, which upon conversion of $PGF_{2\alpha}$ to PGE_2 may inhibit or facilitate exocytosis, respectively. The relative proportion of PGE_2 and $PGF_{2\alpha}$ synthesized by synaptic vesicles may contribute, therefore, to the overall modulation of neurotransmitter release.

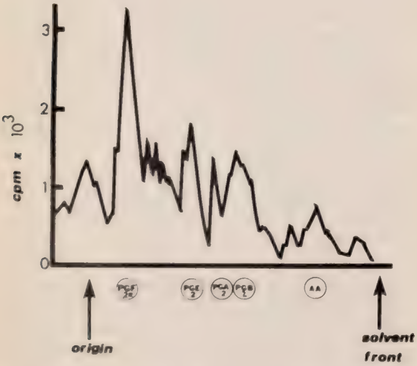

FIG. 1. Radiometric scan of a thin-layer chromatogram of synaptic vesicle arachidonic acid metabolites. Prostaglandin standards that chromatographed with the peaks are indicated.

It has been hypothesized that PGE_2 is produced postsynaptically and is transported to the presynaptic terminal where it exerts its inhibitory effect (34). This model does not explain the mechanism of PGE_2 inhibition. Also, it is questionable

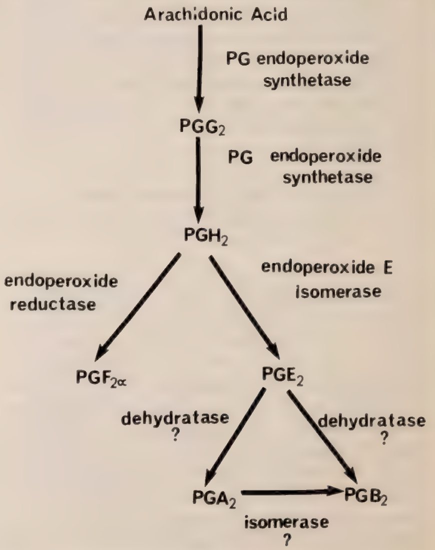

FIG. 2. Proposed metabolic pathway of arachidonic acid in synaptic vesicles.

whether such a process could occur in a reasonable period of time to exert a significant physiological role. The demonstration of presynaptic PGE_2 production by synaptic vesicles in the membranal vicinity of PLA_2, upon which PGE_2 events exert feedback inhibition, may explain how PGE_2 could exert an immediate modulatory function.

We also have demonstrated that synaptic vesicle PLA_2 is slightly activated by cAMP (18). Cyclic-AMP is a nucleotide of key importance in neuromodulation (35) which has been demonstrated to facilitate neurotransmitter release (36). Cyclic-AMP led to a 50% activation of synaptic vesicle PLA_2 activity; however, in conjunction with ATP it led to a 250% activation (Table I). The difference in cAMP stimulation in the presence or absence of ATP led us to speculate that a cAMP-dependent protein kinase may be involved. Cyclic-AMP-dependent membrane protein phosphorylation in synaptic vesicles was studied under standard conditions (37). Autoradiograms of synaptic vesicle phosphorylation in the presence and absence of ATP and cAMP are demonstrated in Figure 3. There is a baseline level of phosphorylation in the absence of cAMP. In the presence of cAMP, proteins with the following M_rs were phosphorylated: 175K, 100K, 80K, 57K, 55K, 53K, 40K and 30K. The 40K phosphorylated protein was of particular significance. Hirata (38) reported the presence of a 40K phosphorylated protein in neutrophils called lipomodulin. Lipomodulin inhibits PLA_2 activity. If lipomodulin is phosphorylated by either Ca^{2+} or cAMP, its inhibition on PLA_2 is released (38). Cyclic-AMP and ATP may have led to higher PLA_2 activity by phosphorylating a 40K protein in synaptic vesicles which may be lipomodulin, thereby releasing its inhibition of PLA_2. Calcium, which was included with cAMP and ATP in the PLA_2 assay, is known to inhibit cAMP-dependent kinases (39). It is possible , therefore, that the kinase may be dependent on Ca^{2+} and on cAMP as has been implicated in another brain kinase system (40). Of the other synaptic vesicle proteins phosphorylated by cAMP, the 80K protein is highly concentrated in synaptic vesicles (41). This protein is activated by cAMP (42) and is involved directly in fusion of the synaptic vesicle with the presynaptic membrane (43). Phosphorylation of proteins with M_rs of 55K also have been demonstrated to be involved in exocytosis (15). Cyclic-AMP, therefore, possibly may modulate neurotransmission in several ways. First, it may directly activate synaptic vesicle PLA_2. It also may activate a cAMP-dependent protein kinase leading to protein phosphorylation. Phosphorylation of lipomodulin may lead to release of PLA_2 inhibition with resultant increase in PLA_2 activity. Phosphorylation of other synaptic vesicle membrane proteins may lead directly to synaptic vesicle fusion independent of a PLA_2 mechanism. The precise mechanism of phosphorylation-induced fusion remains to be elucidated.

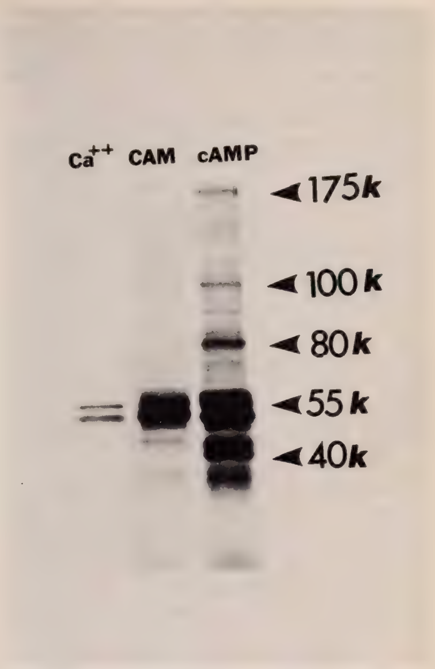

FIG. 3. Autoradiogram of synaptic vesicle proteins incubated in the presence of 1.6 μM γ^{32}-ATP. Gels were analyzed by 5%–15% SDS polyacrylamide gel electrophoresis. The gels were dried and autoradiography was performed using Kodak NS-5T film. Conditions included calcium (Ca^{2+}), calcium and calmodulin (CAM), or $MgCl_2$ and cAMP (cAMP).

How is cAMP related to Ca^{2+}-induced exocytosis? Adenylate cyclase is located in the presynaptic membrane (44). Calcium/calmodulin has been demonstrated to activate adenylate cyclase (19). It may be possible, therefore, that Ca^{2+}/calmodulin stimulation of presynaptic membrane adenylate cyclase leads to the production of cAMP, which may then exert its multiple neuromodulatory effects. The levels of cAMP are controlled as well by a cytoplasmic Ca^{2+}/calmodulin-dependent phosphodiesterase (44, 45) which catalyzes the metabolism of 3′,5′-cAMP to 5′-AMP.

Synaptic vesicles also possess endogenous

Ca^{2+}/calmodulin-dependent protein kinase activity that upon activation lead to synaptic vesicle membrane phosphorylation concomitantly with neurotransmitter release (15). The protein phosphorylation pattern of our brain synaptic vesicle preparation—incubated in the presence of ATP and various conditions as described (37)—is demonstrated in Figure 3. Proteins of 55K and 53K M_r were phosphorylated. In the presence of Ca^{2+} and calmodulin, the putative 40K M_r lipomodulin protein was not phosphorylated under these conditions. The different protein phosphorylation pattern induced by Ca^{2+}/calmodulin compared to that induced by cAMP (Figure 3) implies that the synaptic vesicle has two independent protein kinase systems. It appeared that the 55K and 53K M_r proteins were common substrates to both kinase systems. Activation, therefore, of synaptic vesicle Ca^{2+}/calmodulin protein kinase is another possible mechanism involved in exocytosis (15).

Synaptic Plasma Membrane Phospholipase A_2

We have demonstrated by methods described previously (18) that synaptic plasma membrane (SPM) prepared from rat brain as described by Jones and Matus (46) also manifests PLA_2 activity. The enzyme is Ca^{2+} dependent, has a pH optimum of 7.0, an apparent K_m of 62.0 μM, and a relative V_{max} of 98.0. The enzyme is highly sensitive to Ca^{2+} concentration. In the absence of Ca^{2+}, 0.5% phosphatidylcholine is hydrolyzed. At optimal Ca^{2+} concentration (0.1-1 μM), 13.0% substrate is hydrolyzed. With increasing Ca^{2+} concentrations, PLA_2 activity declines steadily hydrolyzing 1.0% substrate at 0.1 M Ca^{2+}. The effects of calmodulin and PGE_2 on the kinetic parameters of SPM-PLA_2 activity are listed in Table II. Calmodulin decreased both the V_{max} and K_m of the enzyme. A more significant decrease of the latter parameter was noted. If both these kinetic parameters are taken into account by examining the first order rate constant $k(V_{max}/K_m)$ it is apparent that calmodulin stimulated substrate conversion by 638% (Table II). Prostaglandin E_2 slightly inhibited this parameter by 7.7%, as well as almost completely reversing the calmodulin-stimulating effect (Table II). The general effects of calmodulin and PGE_2 on SPM PLA_2 activity, that is, activation and inhibition, respectively, were similar to the effects of these compounds on synaptic vesicle-PLA_2 activity. Activation or inhibition, however, was achieved by modulation of different kinetic parameters. Although the apparent K_m for synaptic vesicle-PLA_2 and SPM-PLA_2 is approximately the same, the relative V_{max} is approximately 50 times higher in the SPM enzyme (Table III). It cannot be surmised, however, that synaptic vesicle-PLA_2 activity merely represents SPM-PLA_2 contamination because both calmodulin and PGE_2 exerted their effects by changes in different kinetic parameters of PLA_2 and because the two enzymes in the two different membrane systems have different pH and Ca^{2+} concentration optima (Table III). Because most PLA_2s are homologous (47), the differences observed in the enzymatic characteristics of synaptic vesicle-PLA_2 and SPM-PLA_2 may be due to different protein lipid interactions in the different membrane systems.

The presence of PLA_2 in SPM with a relatively high level of activity may compound the fusogenic effects of synaptic vesicle-PLA_2 by providing more lysolecithin to enhance membrane fluidity as well as providing more arachidonic acid for prostaglandin conversion. Synaptic vesicles may have a lower baseline substrate conversion rate and a higher Ca^{2+} concentration requirement in order to prevent in vivo vesicle-vesicle fusion.

Other than the possible involvement of SPM, PLA_2 in synaptic vesicle presynaptic plasma membrane fusion, this enzyme may have additional neuroregulatory functions. The presynaptic plasma membrane has neurotransmitter receptors on its external membranal surface facing

TABLE II

Effectors of Synaptic Plasma Membrane PLA_2 Kinetic Parameters

Effectors (concentration)	Apparent K_m (μM)	Relative V_{max}	k mg-1 min-1	% Change k, stimulation (+), inhibition (−)
Ca^{2+} (0.1 – 1.0 μM)	62	98	0.13	control
Calmodulin (1 μM)	1.4	16	0.96	638 (+)
PGE_2 (4.0 nmol)	80	117	0.12	7.7 (−)
Calmodulin (1 μM) + PGE_2 (4.0 nmol)	40.0	88	0.19	46. (+)

Presynaptic plasma membrane (100 μg) was incubated for 30 minutes at 37°C in the presence of 0.1 - 1.0 μM $CaCl_2$ with ^{14}C-arachidonylphosphatidylcholine (0.2 - 2.8 nmol). Kinetic parameters were determined from Lineweaver-Burk transformations of substrate concentration curves (r = 0.96 – 0.99).

TABLE III

Comparison of PLA_2 Characteristics Found in Synaptic Vesicles (SV) and Presynaptic Plasma Membrane (PSM)

Membrane	pH optimum	Ca^{2+} concentration optimum (μM)	K_m (μM)	V_{max} (nmol/mg/hr)
PSM	7	0.1	62	98
SV	9	10.0	60	2

Membrane fractions (100 μg) were incubated at 37°C with ^{14}C-β-arachidonylphosphatidylcholine (.2–4.0 nmol). Kinetic parameters were determined from Lineweaver-Burk transformations of substrate concentration curves.

the synaptic cleft (48). The binding of newly-released neurotransmitters to their respective receptors is involved in feedback inhibition of neurotransmitter release (48). Lipids that surround receptors, the lipid annulus, modulate receptors' three-dimensional structures and regulate receptor-ligand affinity (49). It has been demonstrated that PLA_2 treatment of brain membranes diminishes binding of opiates, dopamine and GABA as well as other ligands (48–50). Thus it is conceivable that activation of presynaptic plasma membrane PLA_2 initially may stimulate neurotransmitter exocytosis by facilitating synaptic vesicle membrane fusion. After neurotransmitter release, PLA_2 activation may alter the affinity of the newly released neurotransmitter for its receptor located on the presynaptic plasma membrane by altering the receptor's lipid annulus and thereby affecting neurotransmitter negative feedback regulation.

The physical state of a lipid domain in which a receptor is situated regulates the lateral mobility of the receptor and, in turn, the interaction of ligand receptor complexes with adenylate cyclase (48). Therefore, activation of SPM-PLA_2 also may regulate neurotransmitter feedback mechanisms by increasing fluidity of the membrane and hence the capacity of neurotransmitter-receptor-adenylate cyclase interactions.

Because SPM-PLA_2 is maximally active at resting Ca^{2+} concentrations, it would seem that this enzyme functions not merely in the regulation of Ca^{2+}-dependent neurotransmitter release and modulation but also is important in membrane lipid metabolism (52).

Correlation of Synaptic Vesicle PLA_2 with Function

We employed synaptic vesicle-vesicle aggregation as a model for synaptic vesicle function (18). When synaptic vesicles were exposed to Ca^{2+} and exogenous PLA_2 (*Vipera russelli*), there was a 250% increase in light scattering within 10 seconds, as detected by nephelometry (Figure 4). This increase was due to aggregation, lysis and possible fusion of synaptic vesicle. Aggregation of vesicles was confirmed by phase-contrast light microscopy (Figures 5, 6). Possible fusion and lysis was confirmed by electron microscopy (Figures 7, 8). The decrease in light scattering immediately following these vesicle membranal changes may be due to vesicle sedimentation. Exogenous lysolecithin induced a synaptic vesicle light-scattering profile similar to that obtained by incubating with exogenous PLA_2 (Figure 4). Thus it was concluded that exogenous PLA_2 hydrolyzed endogenous synaptic vesicle phosphoglycerides with subsequent production of lysolecithin which induced vesicle-vesicle aggregation, lysis and

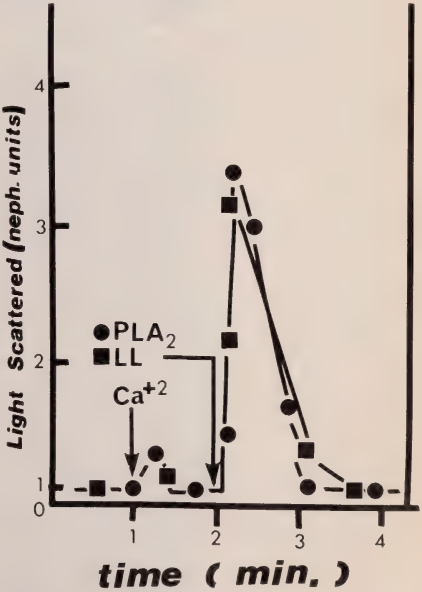

FIG. 4. The effect of CA^{2+} followed by PLA_2 *Vipera russelli* (●) or followed by lysolecithin (■) on synaptic vesicle light scattering. Light scattering in nephelometer units are plotted as a function of time.

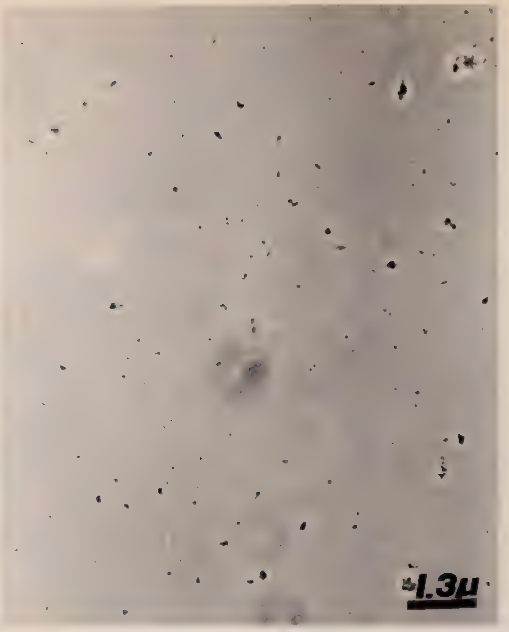

FIG. 5. Phase contrast light microscopy of untreated synaptic vesicles (magnification ×4,330).

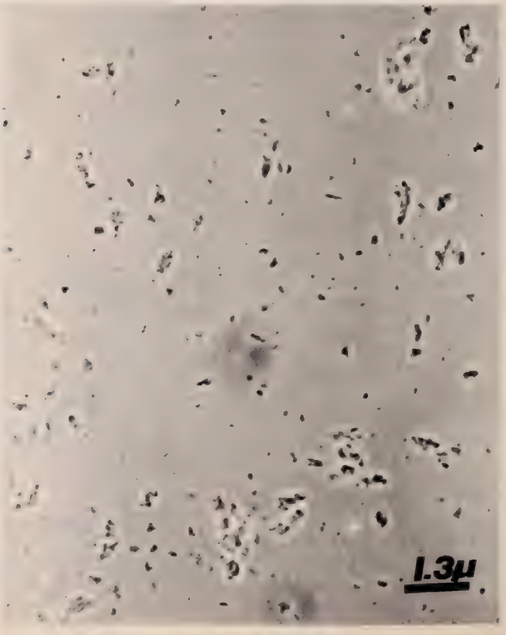

FIG. 6 Phase contrast light microscopy of synaptic vesicles treated with $CaCl_2$ and PLA_2 *Vipera russelli* (magnification ×4,330).

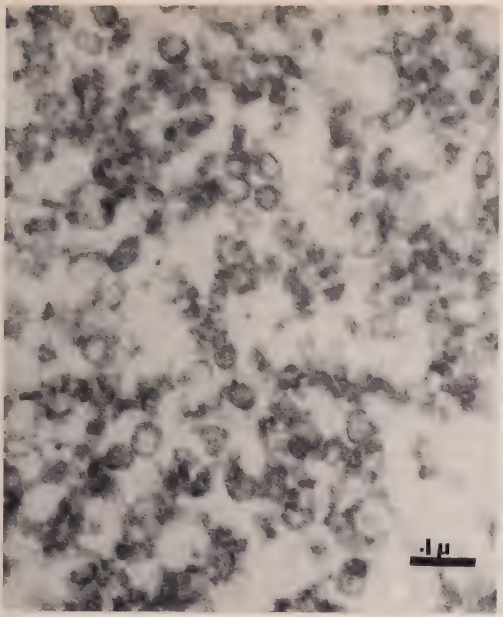

FIG. 7. Electron microscopy of untreated synaptic vesicles (magnification ×120,000).

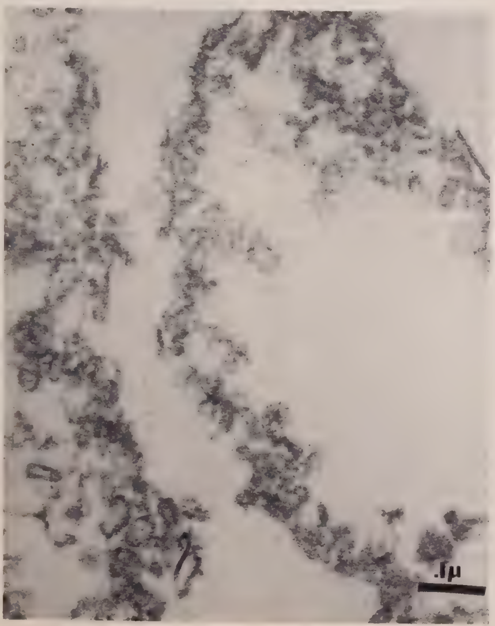

FIG. 8. Electron microscopy of synaptic vesicles treated with $CaCl_2$ and PLA_2 *Vipera russelli* (magnification ×120,000).

possible fusion giving rise to the observed light-scattering profile. Incubation of synaptic vesicles with calmodulin induced a light-scattering profile similar to that observed by incubation with exogenous PLA_2 or lysolecithin. This calmodulin effect was inhibited by PGE_2. It is likely that calmodulin activated endogenous synaptic vesicle PLA_2, leading to enhanced vesicle-vesicle interaction. Preincubation of the vesicles with parabromophenacylbromide or mepacrine, PLA_2 inhibitors (47, 53), prior to calmodulin incubation, diminished calmodulin's stimulating effect (18). Cyclic-AMP and ATP enhanced light scattering only when added concertedly to the synaptic vesicle suspension (18). Both the Ca^{2+} and calmodulin light-scattering effects were potentiated by $PGF_{2\alpha}$ (18). All these effects probably were due in part to activation of endogenous synaptic vesicle-PLA_2 inasmuch as parabromophenacylbromide diminished them.

Modulation of synaptic vesicle-PLA_2 activity therefore was correlated with synaptic vesicle function. This model represented vesicle-vesicle behavior under in vitro conditions as opposed to vesicle-axonal membrane interaction found in vivo. Despite the limitations of this model, our findings buttress the hypothesis that modulation of synaptic vesicle-PLA_2 may be one of the controlling factors in neurosecretion.

Presynaptic Grid and Vesicle Orientation

In the central nervous system, the presynaptic grid is on the cytoplasmic side of the presynaptic membrane and consists of an assembly of dense projections which are arranged in a triagonal lattice and interconnected by filamentous cross-bridges (54). The holes of the grid have roughly the dimensions required to accomodate synaptic vesicles and to align them with the presynaptic membrane to undergo exocytosis. The tubulin molecules endogenous to synaptic vesicles may work in concert with the grid to produce a precise vesicle orientation. Vesicle orientation seems to be a general phenomenon involved in secretion. Satir demonstrated in the species *Tetrahymena pyriformis* that secretory vesicles must be oriented in an exact way in order for secretion to occur (56). Why is orientation necessary? Perhaps all the enzymes in synaptic vesicles together with those located in the presynaptic membrane must be oriented in a certain manner. The concerted action of a host of enzymes can lead to protein and lipid changes in precise membranal regions to bring about controlled quantal neurotransmitter release. This hypothesis is supported by the recent finding that lateral diffusion of lipids in membranes is area restricted (57).

Synaptic Vesicle Ca^{2+} + Mg^{2+} -ATPase

Because exocytosis is initiated by Ca^{2+}, the most efficient means of terminating the reaction is to reduce the axonal Ca^{2+} concentration. This may be achieved primarily by mitochondria (58). Synaptic vesicles also sequester Ca^{2+} by virtue of calmodulin-stimulated Ca^{2+} + Mg^{2+}-ATPase (59, 60). The level of this Ca^{2+} + Mg^{2+}-ATPase activity is very low compared to other systems. The significance of this ATPase might be to produce a local decrease of Ca^{2+}-ion concentration in the surrounding milieu of the synaptic vesicle to produce an immediate termination of Ca^{2+}-mediated exocytosis. Thus calmodulin which stimulates a host of enzymes which initiate exocytosis, also stimulates an enzyme capable of terminating exocytosis. In fact, Scatchard analysis of radio-labeled calmodulin binding to synaptic vesicles confirmed that calmodulin is capable of binding to multiple sites on the synaptic vesicle, therefore exerting multiple effects (60).

The dynamic relationship between many of the presynaptic events hypothesized to be involved in regulation of presynaptic neurotransmission is summarized in Figure 9. The key to initiation of neurotransmitter release is an increase of axon terminal Ca^{2+}-ion concentration. Calcium, once it enters the presynaptic terminal, may act directly on synaptic vesicles to induce fusion, or indirectly via calmodulin to activate actomyosin, PLA_2, and the Ca^{2+}/calmodulin-dependent protein kinase to induce apposition and fusion of the synaptic vesicle with the presynaptic membrane. Calmodulin stimulation of both presynaptic adenylate cyclase and cytoplasmic phosphodiesterase (14, 61) balances the levels of cAMP. Cyclic-AMP may directly activate cAMP-dependent protein kinase leading to the phosphorylation of protein directly involved in membrane fusion, and possibly lipomodulin, which may activate PLA_2. Cyclic-AMP also may directly activate synaptic vesicle PLA_2. Both synaptic vesicle- and SPM-PLA_2 activation lead to production of lysolecithin and subsequently PGE_2 and $PGF_{2\alpha}$. Adenylate cyclase may be activated by PGE_2 (23), leading to an increase of cAMP. Also, PGE_2 may inhibit synaptic vesicle-PLA_2. Synaptic plasma membrane-$PGF_{2\alpha}$ may stimulate synaptic vesicle PLA_2. Calmodulin leads to activation of [Ca^{2+} + Mg^{2+}]-ATPase leading to Ca^{2+} sequestration in the immediate vicinity of the vesicle and consequently inhibition of the entire process which is Ca^{2+} dependent. It is

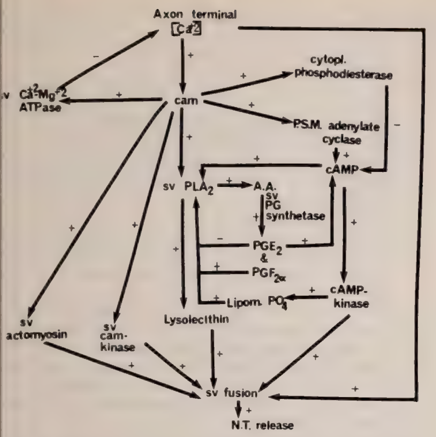

FIG. 9. Scheme of events proposed for Ca^{2+}-mediated exocytosis of neurotransmitter from axon terminals. Plus (+) indicates stimulation, negative (−) indicates inhibition. SV = synaptic vesicle, PSM = presynaptic plasma membrane, cam = calmodulin, PLA_2 = phospholipase A_2, A = arachidonic acid, lipom = lipomodulin, cam-kinase = calcium/calmodulin dependent protein kinase, cAMP-kinase = cAMP dependent protein kinase, N.T. = neurotransmitter.

evident that the mechanism of Ca^{2+}-induced exocytosis may be due to a multiplicity of events rather than the direct action of Ca^{2+} as previously hypothesized (16).

The precise mechanism whereby calmodulin differentially activates a variety of enzymes involved in the stimulation and inhibition of synaptic vesicle exocytosis, and the mechanism whereby the different enzymes, nucleotides, lipids and proteins function concertedly to modulate neurotransmitter release await elucidation.

Enzymatic control of neurotransmission has been criticized on the ground that it would not be fast enough to bring about neurotransmitter release in the required time span of approximately 100 microseconds (62). It may be possible that the concerted and integrated involvement of the numerous enzymatic and non-enzymatic processes discussed may bring about neurotransmitter release within this time limit.

Acknowledgments

The authors thank John Morgan for his editing and preparation of this manuscript.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February 1983
Printed in U.S.A.

Modulation of Presynaptic Neurotransmission

II: Theories of the Mechanism of Synaptic Vesicle Membrane Retrieval by the Coated Pit/Vesicle Pathway

NATHAN MOSKOWITZ, PH.D., AND SAUL PUSZKIN, PH.D.

Abstract

A model for the molecular mechanisms of synaptic vesicle retrieval from presynaptic plasma membrane is proposed, specifically, that activation of an endogenous, coated membrane, Ca^{2+}/calmodulin-dependent protein kinase, leads to phosphorylation of membrane proteins, inducing protein-conformation changes which allow clathrin to recognize a particular site and attach to the membrane to form coated pits. Other proteins may be retrieved selectively from the membrane by being linked to these phosphorylated proteins. The mechanism of coated vesicle transformation from coated pits may be the result of phospholipase A_2 activation on both sides of the coated membrane. Fatty acids liberated by phospholipase A_2 activation could provide a localized acidic milieu promoting clathrin polymerization into lattices. A protein kinase-phosphatase system would explain the reversibility of clathrin-membrane interactions. A host of endogenous coated membrane enzymes may be involved in the regulation of selective uptake and regeneration of synaptic vesicle membrane ensuring the continued flow of neurotransmitter release.

Introduction

It has been postulated that after releasing quantal packets of neurotransmitter into the synaptic cleft, synaptic vesicles are retrieved from the presynaptic plasma membrane by the coated pit/vesicle pathway (1, 2). Coated pits and vesicles are characterized morphologically by the presence of a coat (3) consisting primarily of clathrin, a 180K molecular weight (M_r) protein (4). The synaptic vesicle is retrieved selectively by the coated pit, a region of the plasma membrane, which invaginates, pinches off and becomes a coated vesicle. The coated vesicle then sheds its coat to become a synaptic vesicle (5). This model explains many of the observed presynaptic events (5) and is illustrated in Figure 1. Using this model as the starting point, we have addressed the regulation of (a) clathrin recognition and insertion into specific synaptic vesicle membrane proteins; (b) clathrin-clathrin association to form a coat lattice; and (c) coated vesicle formation from coated pits.

Clathrin Insertion into Membranes; Selectivity of Coated Pit Formation

The hypothesis that coated pits selectively retrieve a specific protein bound by its specific receptor in areas destined for endocytosis (6) raises two questions: How does clathrin recognize and interact with different proteins? What governs the reversible nature of clathrin recognition? We have attempted to answer these questions (7). Coated vesicles were incubated in the presence of $[\gamma^{32}P]$-ATP under various conditions and the protein population resolved by 5%–15% sodium-dodecyl-sulfate (SDS) polyacrylamide electrophoresis. Autoradiograms of the resolved proteins are shown in Figure 2. Significant phosphorylation occurred only in the presence of Ca^{2+} and calmodulin. The phosphorylated proteins had M_rs of 175K and 55K. Since exogenous kinase was not added to the assay, we concluded that coated vesicles have an endogenous Ca^{2+}-calmodulin-dependent protein kinase. Immunological and immunocytochemical studies identified the protein kinase as an approximately 30K M_r protein doublet (7). This 30K protein invariably copurifies with clathrin (8). Inasmuch as protein phosphorylation is known to be a key regulator of cellular events inducing protein-conformation changes (8), we suggest that the ~30K protein acts as a protein kinase in the presence of Ca^{2+} and calmodulin, phosphorylating the 175K and 55K proteins to induce conformational changes which may allow these proteins to recognize clathrin.

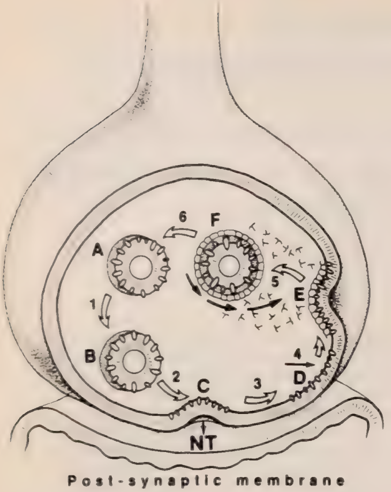

FIG. 1. Model of axon terminal depicting a synaptic vesicle (A) which upon stimulation (1) moves closer to the presynaptic membrane (B) until it fuses with the membrane (2), becoming incorporated into it (C). This process results in the release of neurotransmitter (NT) into the synaptic cleft. Upon selectivity and crosslinking of specific synaptic vesicle membrane proteins (3), cytoplasmic clathrin subunits (Y-shaped structures) insert into (4) the selected membrane (D) to become a coated pit (E). The coated pit invaginates, pinches off (5), and becomes a coated vesicle (F). The coated vesicle subsequently sheds its clathrin coat (6) and once again becomes a synaptic vesicle (A).

Thus clathrin, under these conditions, may initiate membrane invagination. Calmodulin has been implicated in the recruitment of clathrin to membranes to form coated pits (10). The Ca^{2+}/calmodulin-dependent phosphorylation of membrane proteins may be the mechanism by which this is accomplished.

Transglutaminases crosslink proteins into the coated pit by catalyzing the formation of E(γ-glutamyl)-lysine bonds between proteins and coupling of amines and diamines to the γ-carbonyl residues of glutamine (11). This has been confirmed by the inhibition of coated pit/vesicle-mediated endocytosis in the presence of transglutaminase inhibitors (12). Once selected proteins are crosslinked, clathrin may bind to the phosphorylated 175K and 55K M_r proteins which possibly are located at regular intervals between the specific synaptic vesicle proteins destined for endocytosis. Transglutaminase crosslinking would assure that all the proteins form a discrete entity. This would mean that clathrin would have to recognize only the 175K and 55K M_r synaptic vesicle proteins. The other synaptic vesicle proteins would be selectively retrieved in the coated pit by virtue of transglutaminase crosslinking. Selectivity of synaptic vesicle proteins included in the pit would be mediated, therefore, mostly by transglutaminase activity and, to a limited extent, by clathrin recognition of proteins. The fact that coated vesicles do not have cAMP-dependent kinase activity (Figure 2) whereas synaptic vesicles do (7), implies that the synaptic vesicle, cAMP-dependent protein kinase is one protein complex that is not selectively retrieved by coated vesicles. Thus, the mechanism of transglutaminase protein selectivity remains to be solved.

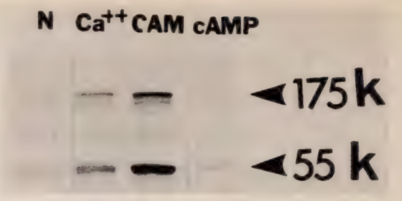

FIG. 2. Autoradiogram of coated vesicle proteins incubated in the presence of 1.6 μM γ^{32}P-ATP. Gels were analyzed by 5%–15% SDS polyacrylamide gel electrophoresis. The gels were dried and autoradiography was performed using Kodak NS-56 film. Incubation conditions included (N) no reagents added, (Ca^{2+}) calcium, (CAM) calcium and calmodulin, and (cAMP) $MgCl_2$ and cAMP.

Coated Vesicles from Coated Pits

After clustering of specific proteins and the insertion of clathrin into the membrane to form coated pits, the coated pits invaginate, pinch off and become coated vesicles. It has been postulated that coated pits are transformed into coated vesicles when coated pit clathrin lattices arranged mostly in hexagons are transformed into pentagons, causing increased curvature and creating a force sufficient to pinch the coated pits off from the membrane (13). The phenomenon of hexagon-to-pentagon transformation is documented by electron microscopy (5). If this is the mechanism of coated vesicle formation, what initiates this transformation and what is the nature of this force? Our recent studies form the basis of an alternative hypothesis. Coated vesicles were assayed for phospholipase A_2 (PLA_2) activity as described (14) and found to have a pH optimum of 9.0, to be Ca^{2+} dependent, to have an apparent K_m

of 3.5 μM and a relative V_{max} of 6.86 nmol/mg/hour.

Preliminary results indicate that calmodulin activates coated vesicle PLA_2. It is possible that the activation of PLA_2 on both sides of the coated pit may create nicks in the membrane by increasing fluidity due to phospholipid hydrolysis and lysolecithin release. The coated pit membrane, separated on both sides from the rest of the membrane, may then reseal to form a coated vesicle. The change from hexagons into pentagons observed in the coat apparatus merely may be a manifestation of coated pit/vesicle formation rather than the driving force behind it. It has been demonstrated that exposure of axon terminals to β-bungarotoxin, a PLA_2, leads to an immediate depletion of synaptic vesicles from axon terminals and to the formation of coated vesicles (5). Moreover, the inhibition of coated-pit-mediated epidermal growth factor internalization (15) by quinacrine and parabromophenacylbromide, PLA_2 inhibitors (16, 17), further strengthens the hypothesis that PLA_2, may be involved in coated pit/vesicle-mediated endocytosis. The demonstration and partial characterization of endogenous PLA_2 activity in coated vesicles implies that coated pit PLA_2 activation may be one of the mechanisms involved in the transformation of coated pits to coated vesicles.

In the coated vesicle, clathrin forms a lattice of alternating rings of hexagons and pentagons (13). What leads to clathrin-clathrin interaction? Purified clathrin in the absence of membrane or any source of energy polymerized into latticelike basket structures at or below pH 6.5 (19). The mechanism of this interaction in an acidic medium is not well understood. The activation of PLA_2 in coated vesicles could lead to the formation of lysolecithin as well as free fatty acids in the immediate vicinity of the coated pit. Thus activation of coated pit PLA_2 may lead to the creation of membranal nicks via lysolecithin production, as well as clathrin-clathrin lattice polymerization due to the localized acidic milieu created by the liberated fatty acids.

Coated Vesicle Prostaglandin Synthetase

We investigated the metabolic fate of liberated coated vesicle arachidonic acid. Coated vesicles were incubated with arachidonic acid (specific activity 55.8 mCi/nmol). The reaction was stopped and processed as described (20). A radiochromatogram scan of the products resolved on TLC plates is shown in Figure 3. The radioactive peaks co-chromatographed with prostaglandins E_2, $F_{2\alpha}$, A_2, B_2 and thromboxane B_2 standards. It appeared that most of the arachidonic acid was metabolized and that endogenous coated vesicle prostaglandin synthetase is very active. The major product produced appeared to be thromboxane B_2. The possible metabolic pathway of arachidonic acid in coated vesicles based on this preliminary data is shown in Figure 4. This pathway is similar to that found in synaptic vesicles except that coated vesicles also are capable of synthesizing thromboxane A_2, which is highly labile (T 1/2 = 30 sec-

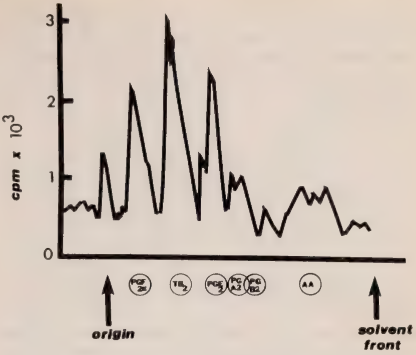

FIG. 3. Radiometric scan of thin layer chromatogram of coated vesicle arachidonic acid metabolites. Prostaglandin and thromboxane standards that co-chromatographed with the peaks are indicated.

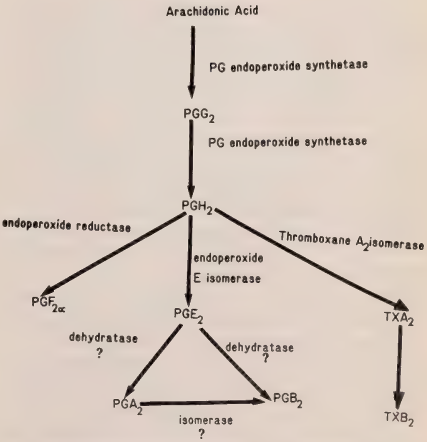

FIG. 4. Proposed metabolic pathway of arachidonic acid in coated vesicles based on preliminary results.

onds) and is converted to thromboxane B_2 (21). The functions of these products remain to be investigated. Whether PGE_2 and $PGF_{2\alpha}$ modulate PLA_2—as they do in synaptic vesicles—must also be determined.

Coated Vesicle Disassembly

We believe that the continued existence of coated vesicles is dependent on a sustained phosphorylated state of the coated vesicle proteins. This state depends on the presence of Ca^{2+}. Coated vesicles have a $[Ca^{2+} + Mg^{2+}]$-ATpase which is calmodulin dependent (22,23). Activation of this enzyme may lead to the local sequestration of Ca^{2+} into coated vesicles with eventual disassociation of calmodulin from the ~30K protein kinase. Protein phosphatases usually associated with protein kinases hydrolyze phosphates from proteins (24). The activation of a protein phosphatase may lead to dephosphorylation of the 175K and 55K M_r proteins with the subsequent return of these proteins to their native conformations which do not recognize clathrin. Under these conditions, clathrin may detach from the proteins and become part of the soluble cytoplasmic clathrin pool (25). Morphological evidence suggests that the denuded coated vesicle is transformed somehow into a synaptic vesicle (5). This is substantiated by similar polypeptide compositions of both vesicles (26). The mechanism of this transformation requires elucidation.

Vesicle Mobility

Vesicle mobility can be inhibited by cytochalasin B and colchicine, actin and tubulin disruptors, respectively (27–29). Both synaptic and coated vesicles have proteins with M_rs corresponding to actin and tubulin. Whether endogenous vesicle contractile proteins or cytoplasmic contractile proteins impinging on synaptic and coated vesicles are involved in their movement is not clearly established. It is interesting to speculate on the role of prostaglandins and thromboxanes produced by these vesicles with respect to vesicle mobility.

Whole cells, for example neutrophils and leukocytes, undergo chemotaxis, that is, they move in response to a chemical gradient. The basis of directional movement involves (a) the interaction of a chemoattractant with the plasma membrane; (b) an altered transmembrane potential; (c) changes in cyclic nucleotide metabolism; and (d) oxygen uptake as well as PLA_2 activation (30). Polarity of cells is established by reorganization of cytoskeletal contractile elements (30) causing both synaptic and coated vesicles to undergo directed movement: synaptic vesicles to the plasma membrane and coated vesicles away from the plasma membrane. In other cells, coated vesicles must move from the golgi to the plasma membrane or shuttle to lysosomes (31, 32).

Contractile elements are involved in moving these vesicles, as inhibition of these movements by contractile protein disruptors indicates. Still, questions remain. How is directionality of vesicle movement established? Are vesicles capable of chemotaxis? All the necessary elements required for chemotaxis are present, that is, PLA_2, protein kinase, ion transport potential, and even cytoskeletal elements. It is of interest that TXB_2, and various prostaglandins are produced by and are chemotactic for leukocytes, polymorphonuclear and other cells (33–36). Is it possible that one of the functions of prostaglandins and thromboxanes generated by synaptic and coated vesicles is to interact with other vesicles and/or other organelles/membranes and initiate vesicle chemotaxis? Perhaps selective activation of actin, myosin, and tubulin on one pole of the vesicle or polar clustering of these proteins could bring about directionality of vesicle movement. Further experimentation is needed.

Summary

Figure 5 summarizes the major events involved in the retrieval of synaptic vesicles by the forma-

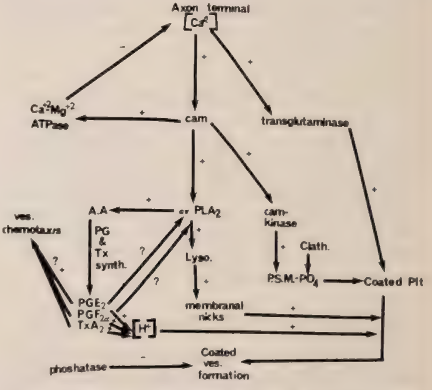

FIG. 5. Scheme of events proposed for Ca^{2+}-mediated coated pit and vesicle formation, and coated vesicle dissociation. Plus (+) indicates stimulation, minus (−) indicates inhibition, cam = calmodulin, cam-kinase = Ca^{2+}/calmodulin dependent protein kinase, cv = coated vesicle, ves = vesicle, A.A. = arachidonic acid, PLA_2 = phospholipase A_2, PSM = presynaptic plasma membrane, clath = clathrin, Pg & Tx synth = prostaglandin and thromboxane synthetases, Lyso = lysolecithin.

tion of coated pits/coated vesicles. Calcium and calmodulin initiate the entire process. Coated pit formation may be the result of Ca^{2+} stimulation of transglutaminase and Ca^{2+}/calmodulin stimulation of PLA_2 and coated vesicle protein kinase activities. Stimulation of PLA_2 leads to the release of arachidonic acid, which is metabolized to various prostaglandins and thromboxanes, all of which may contribute to a local acidic milieu facilitating clathrin-clathrin interaction. Furthermore, these compounds possibly may be involved in vesicle mobility. Calmodulin may lead to the disassembly of coated vesicles by stimulating $[Ca^{2+} + Mg^{2+}]$-ATPase, thus sequestering Ca^{2+}. Stimulation of a protein phosphatase would dephosphorylate proteins and further facilitate coated vesicle disassembly. Invoking a phosphorylation/phosphatase system may explain the observed reversibility of clathrin-membrane interaction. All these mechanisms may be integrated to bring about retrieval of the synaptic vesicle, thus ensuring the continued regeneration of synaptic vesicles and continued propagation of neuronal chemical signals.

Acknowledgments

The authors thank Christine Ores for her electron microscopy and John Morgan for editing and preparing this manuscript.

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Submitted for publication April 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Puberty and Resonance: A Hypothesis

STEVEN LEHRER, M.D.

Abstract

A new mechanism for puberty is proposed. Puberty appears to result from the interaction of two physiologic oscillators within the hypothalamus: the arcuate nucleus, which produces the gonadotropin-releasing hormone, and the suprachiasmatic nucleus, which is a master oscillator that regulates many circadian rhythms. Puberty results when the frequency of the arcuate nucleus has slowed sufficiently to resonate with a harmonic of the suprachiasmatic nucleus rhythm. The onset of puberty is earlier in blind girls and rats reared in darkness because they have circadian rhythms which are more rapid than usual. Therefore, the frequency of the arcuate nucleus does not have to slow as much to resonate with the same harmonic of the suprachiasmatic nucleus rhythm, and puberty can occur at an earlier age. The proposed mechanism also accounts for the occurrence of luteinizing hormone pulses only during sleep in early puberty, and for the elevation of gonadotropins at birth.

Puberty, the transitional period between childhood and adulthood, is accompanied by the appearance of secondary sexual characteristics and the achievement of fertility. In mammals, the central nervous system exercises the only restraint to puberty onset. This neuroendocrine control is mediated by the gonadotropin releasing hormone (GnRH) secreting neurons in the arcuate nucleus of the hypothalamus (1). For many years, a "gonadostat" or feedback mechanism was believed to explain the relatively sudden onset of puberty. Recent evidence, however, has cast doubt on the gonadostat hypothesis; few investigators in the field today still believe that it is correct. This article proposes a new explanation for the onset of puberty, the physical phenomenon of *resonance*.

The Gonadostat Hypothesis

The basis of the gonadostat hypothesis is the pituitary hypertrophy that occurs after castration. This phenomenon was familiar to physiologists at the beginning of this century and is clearly described in a comprehensive article on the pituitary written by Harvey Cushing in the autumn of 1909 (2, 3). In 1936 Hohlweg found that estradiol treatment was more effective suppressing castration hypertrophy in prepubertal rats than in adult rats (4). Hohlweg's observation provided the rationale for the view, later put forward by Ramirez and McCann (5), that puberty is caused by a sudden decrease in sensitivity of the hypothalamic-pituitary unit to sex hormone feedback. The immature gonads were known to produce small amounts of sex steroids, even in very young animals. These hormones were believed to inhibit the hypothalamic-pituitary production of the gonadotropins, follicle stimulating hormone (FSH), and luteinizing hormone (LH). It was hypothesized that around the time of puberty, the hypothalamic-pituitary axis lost its sensitivity to such small amounts of sex steroids, a sudden outpouring of gonadotropins occurred, and puberty was the result. In other words, the "gonadostat" had been reset and would only respond to the feedback effect of much higher levels of sex hormones.

In the past few years, assay techniques that make possible the continuous measurement of gonadotropin levels have cast doubt on the gonadostat hypothesis. These measurements reveal that LH, for example, is elevated not only at puberty but also at birth in both rats and humans (Fig. 1). In humans, LH falls between the ages of two and four, then rises again at puberty. This fluctuation, which corresponds with the period of

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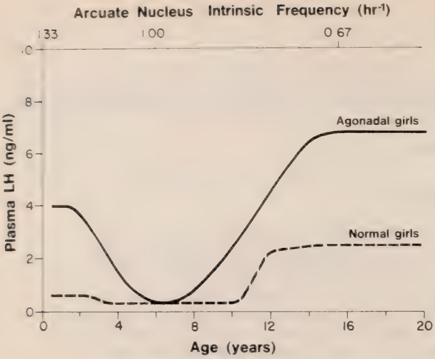

FIG. 1. (Modified from Grumbach, reference no. 1): The high LH levels at birth and puberty, in both normal and agonadal girls, can be accounted for by a continually slowing arcuate nucleus intrinsic frequency after birth.

infant sexuality and subsequent latent period posited by Freud (6), is especially prominent in agonadal children; it cannot be explained adequately on the basis of the gonadostat hypothesis. Further, the sensitivity of the pituitary-hypothalamic axis does not appear to change appreciably during development (7). These observations imply that the phenomenon observed by Hohlweg is a result rather than a cause of puberty onset (8).

Fertility and Circadian Rhythms

The reproductive cycle of mammals is closely related to the 24-hour light : dark cycle and circadian rhythms (9). For example, during long nights and short days or after blinding, gonadal atrophy will occur in the Syrian golden hamster, *Mesocricetus auratus*. This phenomenon has been shown to be mediated by stimulation of the pineal gland (10). Moreover, the four-day estrus cycle of hamsters is closely coupled to the length of the light : dark cycle. A normal hamster living in a 24-hour light : dark cycle has an estrus cycle of 96 hours (4 × 24); whereas a hamster maintained under constant dim illumination with a free running circadian rhythm of 24.5 hours has an estrus cycle of 98 hours, that is, 4 × 24.5 (9).

Puberty, too, is affected by the light:dark cycle. Blind girls have their menarche earlier than sighted girls (11, 12), and rats reared in constant darkness have vaginal opening earlier than rats reared in an eight hour light : sixteen hour dark cycle (13). Other investigators have attributed this acceleration of puberty to a pineal effect. However, such an effect would be paradoxical, since blindness or darkness stimulates the pineal, resulting in gonadal atrophy (10).

A more plausible explanation is that acceleration of the normal 24 hour circadian rhythms has accelerated puberty. These rhythms are generated in rats, hamsters, and probably higher mammals as well by a hypothalamic structure, the suprachiasmatic nucleus or SCN (14). The SCN rhythm is exactly synchronized with the external light-dark cycle by impulses received from the eyes through a retinohypothalamic projection. In a blind animal or an animal kept in constant darkness or constant dim illumination, the SCN rhythm is free running, that is, somewhat greater or less in frequency than one cycle in 24 hours. The SCN is believed to be a master clock or *zeitgeber*, probably driving other physiologic rhythms, including plasma corticosterone levels and pineal N-acetyltransferase levels in rats. In blinded animals these rhythms are also free running, though synchronized with each other (15).

Blind adult human beings are known to have a free running frequency of about one cycle in 25 hours (16), but the free running frequency of children is unknown. One may, therefore, suggest that the free running frequency of a child is greater than one cycle in 24 hours—perhaps one cycle in 21 hours—and slows with age. Such slowing with age has recently been demonstrated in hamsters (17).

There are two possible ways of explaining how accelerated circadian rhythms could accelerate puberty. One way is to postulate that an animal needs a certain critical number of rhythmic stimuli to trigger puberty. In the rat, which has vaginal opening at about 38 days, 38 such stimuli would obviously be necessary. But in a rat on a 21-hour light : dark cycle, 38 stimuli could be given in about 33 days (that is, 21/24 × 38), thus accelerating puberty (Fig. 2), a fact which has been demonstrated experimentally (18). Attractive though this explanation may be, it fails to account for two important facets of the childhood-puberty-adulthood sequence: (a) the elevation of gonadotropins at birth, and (b) the pulses of LH occurring every 1½ hours only during sleep at the onset of puberty in humans; these pulses later occur continuously every 1½ hours throughout the day (19). However, the physical conditions of oscillation and resonance can explain all of these factors.

Oscillation and Resonance

Work by Knobil and others suggests that the gonadotropin-releasing hormone secreting cells of

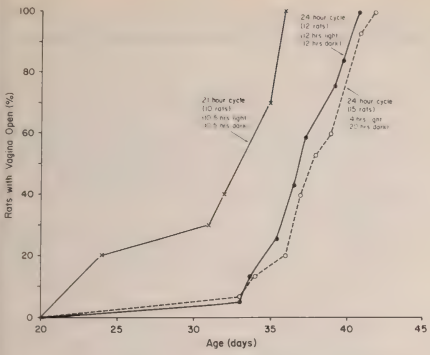

FIG. 2. Rats reared on a 21-hour light : dark cycle (10.5 : 10.5) had vaginal opening significantly ($p < 0.01$) earlier than rats reared on two variants of a 24-hour light : dark cycle (12 : 12 or 4 : 20).

the arcuate nucleus are an independently functioning oscillator with their own intrinsic or free-running frequency (20, 21). But in a normal, intact animal, the oscillation of the arcuate nucleus interacts with the *zeitgeber,* the SCN. As the animal approaches puberty, the frequency of the arcuate nucleus slows and resonance, which is well documented in animals (22), occurs.

Hormonal surges increase in intensity at this time because in any oscillating system, the amplitude of the oscillations surges to a maximum at resonance. This may be likened to the motion of a swing being pushed periodically. When the pushes occur with a frequency other than the intrinsic one of the swing, the displacement of the swing is rather small. But as the frequency of the pushes approaches the intrinsic frequency of the swing, the displacement of the swing becomes larger and larger. Resonance is said to occur when an oscillating system, be it swing or arcuate nucleus, is acted on by a periodic series of impulses (from the SCN in the case of puberty) having a frequency equal or nearly equal to its intrinsic frequency.

This explanation is most satisfactory if the SCN is postulated to be acting on the arcuate nucleus with an ultradian frequency of one cycle in 1½ hours (that is, 0.67 cycle per hour) rather than one cycle in 24 hours. Such an ultradian frequency is possible according to the laws of physics because it is an integral multiple or harmonic of the fundamental frequency of the SCN (that is, 16 × 1/24). Further, ultradian oscillations of this frequency and the existence of more than one intrinsic frequency are well documented in humans and other animals (22, 23).

An animal on a 21-hour light : dark cycle would have an ultradian rhythm more rapid than 0.67 cycle per hour, since this rhythm is a multiple of and coupled to the SCN rhythm. As a result, the arcuate nucleus rhythm would not have to slow as much for resonance to occur, and puberty would take place at an earlier age (Fig. 3).

The high LH level at birth can also be explained. If the frequency of the arcuate nucleus of an infant is very much higher than in an adult, specifically 1.33 cycles per hour, resonance with the ultradian rhythm of the SCN will occur, since 1.33 cycles per hour is an integral multiple (harmonic) of 0.67 cycle per hour (that is, almost 2 × 0.67). As the frequency of the arcuate nucleus slows between four and eight years of age, resonance is lost and LH levels drop. But when the frequency of the arcuate nucleus has slowed to 0.67 cycle per hour, resonance again occurs, resulting in the gonadotropin surge necessary for secondary sexual development (Fig. 1). The surges at puberty may be greater than the neonatal surges because of the growth and maturation of the brain that have taken place during the interval, or because resonance may not occur as readily at the higher fundamental frequency, 1.33 cycles per hour.

An interesting characteristic of the data in Fig. 1 is the apparent logarithmic slowing of the intrinsic frequency of the arcuate nucleus with time, especially evident in the agonadal girls. The peak LH level in infancy occurs at age 1.6, the minimum at age 5, and the peak pubertal level at

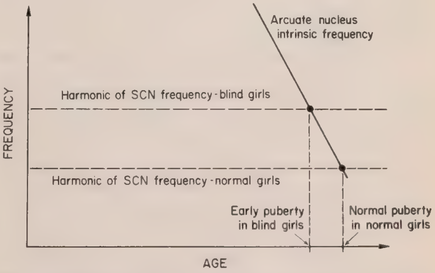

FIG. 3. Blind girls (and rats reared in constant darkness) probably have higher than normal suprachiasmatic nucleus (SCN) frequencies and corresponding harmonics. As a result, the intrinsic frequency of the arcuate nucleus does not have to slow as much for resonance to occur, and puberty can take place at an earlier age.

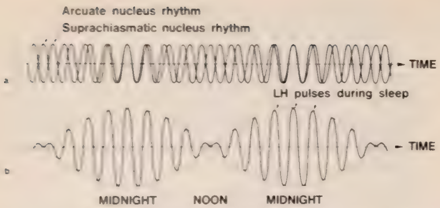

FIG. 4. The beat phenomenon. Two rhythms of slightly different frequencies, shown in (a), combine in (b) to produce a rhythm whose amplitude (broken line) varies periodically with time. This variation may account for the LH pulses which occur only during sleep in early puberty.

age 16 (1); the logarithms for each of these ages are as follows:

age	1.6	5	16	50
log age	0.2	0.7	1.2	1.7

The logarithmic difference between each of these age-points is 0.5. Thus, the next theoretically complete loss of resonance, comparable to that at age 5, would occur at age 50—around the time of menopause.

The mechanism of resonance can account for the LH pulses that occur during sleep in early puberty. At early puberty, the frequency of the arcuate nucleus is very close to the ultradian frequency of the SCN. When two oscillators of very nearly the same frequency interact, the phenomenon known as "beats" will occur (Fig. 4); the rhythms combine to give a rhythm whose amplitude varies periodically with time. Such a mechanism is familiar in mammals, having already been invoked to explain the hormone level variations in the rat estrus cycle (24). In the phenomenon of puberty, the beats correspond with the LH pulses during sleep.

In addition, the beat phenomenon appears to be related to the connection between time of puberty onset in girls and body weight. Very lean girls undergo menarche later than girls with more adipose tissue (25); a specific fat-to-lean mass ratio must be present for the onset of menarche. The resonance mechanism of puberty suggests that extreme leanness increases the frequency of the arcuate nucleus. One would therefore expect that rapid loss of weight in a young postpubertal woman might restore LH "beats" during sleep; this, in fact, has been observed to occur (26).

Thus, as this article attempts to demonstrate, many of the characteristics of puberty can be explained as the simple interaction between two groups of oscillating cells within the brain, the arcuate nucleus and the suprachiasmatic nucleus.

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Submitted for publication March 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Evaluation of a New Cerebral Function Monitor During Open-Heart Surgery

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Abstract

The continuous recording of global cerebral electrical activity by a new type of cerebral function monitor provides a useful supplement to the monitoring of patients during cardiac surgery. The cerebral function monitor uses a filtered and time-compressed signal obtained from a set of disposable parietal electrodes to provide a convenient, simple, inexpensive, and reliable record of global cerebral electrical activity. This study analyzes the utilization of a cerebral function monitor in 170 patients undergoing open-heart surgery. Evaluation of the data indicates the benefits derived from continuous monitoring of the mean global cerebral electrical activity, which may be helpful in optimizing perfusion technique during cardiac surgery. Samples of monitoring tracings and their interpretation are presented.

Introduction

During recent years hypothermia, cardioplegia, hemodilution, and microfiltration; improved anesthetic, perfusion, and surgical techniques; and advances in postoperative care have all combined to decrease morbidity and mortality following open-heart surgery. Progress in monitoring hemodynamic and respiratory parameters has also helped to optimize management of patients undergoing cardiopulmonary bypass (CPB) and increase the margin of safety. The monitoring of cerebral function has not kept pace with advances in other areas (1), however; inadequate cerebral perfusion during CPB leading to either transient or permanent brain dysfunction is still a well-recognized hazard of open-heart surgery (2–4).

Several methods of obtaining information about cerebral function are available. Although invasive techniques for measuring cerebral blood flow, oxygen consumption, metabolic changes, and intracranial pressures are available (4), they are not useful for continuous monitoring of the patient's cerebral status in the operating room because of the increased hazards they present in a heparinized patient. Noninvasive techniques, for example ophthalmodynamometry, oculoplethysmography, anterior ethmoidal artery plethysmography, and radioactive scanning, are also used but are cumbersome and require further evaluation. Monitoring of global cerebral electrical activity (GCEA) currently offers the only continuous, noninvasive method of determining the state of a patient's brain during open-heart surgery.

At present two methods are available for measuring GCEA: the electroencephalogram (EEG) and the cerebral function monitor (CFM). Although the conventional multichannel EEG has been available since the introduction of open-heart surgery, its use in everyday clinical practice in the operating room has been limited by technical, economic, and practical difficulties (3–5). Recently developed power spectrum analysis and automated, computerized EEG monitoring do not solve these problems (6–9). The CFM was originally designed in 1969 by Maynard et al (10) (Devices Limited, Model 4660, Jersey, England). The recording is provided by means of three disposable electrodes attached to

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Portions of this article were presented at the third World Congress on Intensive and Critical Care Medicine, Washington, D.C. (May 1981); the first World Congress on Open Heart Technology, Brighton, England (July 1981); and the Central European Congress of Anesthesiologists, Berlin (Sept 1981).

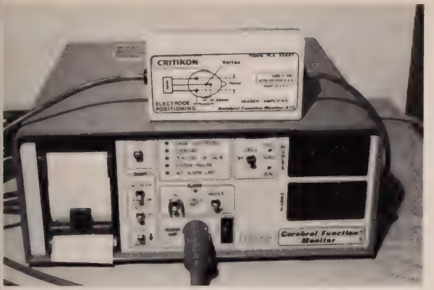

FIG. 1. Critikon Model 870 (weight 13 lbs.).

the scalp giving a continuous tracing of the GCEA level in microvolts and frequency in Hertz. The apparatus is portable and convenient to use and the tracings are easy to interpret. Technical details, basic electronic components, calibration, impedance circuits, and the recorder have been previously described. Our clinical experience with this monitor was reported previously (11–13).

This paper deals with two CFMs, this earlier model produced by Devices Limited and a later, current model produced by Critikon.

Methods and Materials

In this study a newly developed CFM (Critikon Model 870, Critikon Inc., Tampa, Florida) was used (Fig. 1). Microprocessor-based electronics provide enhanced output capabilities with indications of levels of GCEA. The device has two display media: a digital display on the front panel and a graphic display on the strip chart recorder. The recording continuously registers the low, high, and average (mean) levels of GCEA in the range of 0–100 microvolts and the mean frequency in Hertz. Signals can be recorded at two speeds, either 60 or 30 cm/hour. The device has automatic calibration as well as alarms and electrode-status monitors. The basic electronic design, calibration, alarm circuits, and other technical details have been described (14).

The new CFM is about one-half the weight and volume of the earlier model, a contribution of modern electronic technology. Overall, the new model provides a useful display of the GCEA with optimal safeguards. The Critikon Model 870 was used for continuous monitoring of the GCEA in 170 patients undergoing open-heart surgery (Table I).

TABLE I
Open-Heart Surgery Procedures Yielding Data on Cerebral Function Monitor

Type of operative procedure	Number of patients
Coronary artery bypass graft(s) (CABG)	121
CABG + valve replacement	11
Aortic valve replacement	14
Mitral valve replacement	16
Other*	8
Total	170

* Patients in cardiogenic shock after acute myocardial infarct (left ventricular aneurysm or postinfarct ventricular septal defect); each was supported by a pharmacological vasoactive agent and an intra-aortic balloon pump.

Methods

For premedication, a combination of lorazepam, morphine, and atropine or scopolamine was utilized. Prior to induction of anesthesia, all patients were routinely monitored by means of an electrocardiogram for arterial and central venous pressures; in some cases a Swan-Ganz catheter was inserted for further hemodynamic monitoring. Various anesthetic intravenous agents were used for induction of anesthesia: thiopental, diazepam, Sublimaze, ketamine.

Facilitation of intubation was provided by pancuronium, succinylcholine, or d-tubocurarine. Anesthesia was maintained with Sublimaze, morphine, ketamine, halothane, ethrane, and nitrous oxide. Intravenous anesthetic agents were delivered for maintenance with a continuous microinfusion pump (IVAC Co., San Diego, California).

The patients were ventilated mechanically with an Engstrom System 300 (Engstrom L.K.B. Instruments, Inc., Rockville, Maryland) respirator (15) with a minute volume of 10–12 ml/kg/min and controlled with analyses of arterial blood gases. Perfusion was carried out with membrane oxygenators (Travenol) and arterial filters (Pall) and cardiotomy line filters (Pall Biomedical Products Co., Glen Cove, New York), using a Sarns roller pump and calculated flow of 2–2.2 liters/m^2 body surface/min. The pump prime consisted of Normosol R (1800 cc).

A left atrial line and atrial and ventricular pacing electrodes were inserted routinely. After surgical correction was completed, patients were rewarmed to 35°–37°C and removed from CPB. When hemodynamic stability was achieved, the sternotomy was closed and patients were transferred to the cardiac intensive care unit.

The GCEA was continuously monitored (recorded at 60 cm/hour) after the induction of anesthesia until the patient was transferred to the

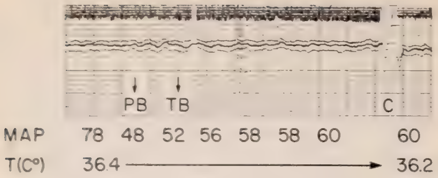

FIG. 2. Recording of global cerebral electrical activity (GCEA). Electronics microprocessor registers low, high, and average (mean) signals of GCEA in microvolts (μV 0-100) at a rate of 2 minutes for each box. The upper portion of the traces indicates simultaneous frequency in Hertz (Hz 0–16). Key: PB, bypass; TB, total bypass; C, calibration; MAP, mean arterial blood pressure; T(C°), midesophageal temperatures.

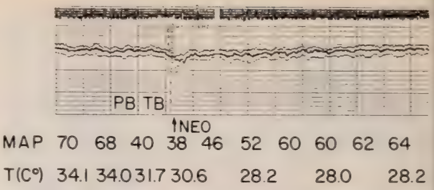

FIG. 3. Recording during partial and total bypass. Demonstration of influence of Neo-Synephrine directly into pump oxygenator or GCEA. Key: PB, partial bypass; TB, total bypass; MAP, mean arterial blood pressure; T(C°), midesophageal temperatures; NEO, Neo-Synephrine.

cardiac intensive care unit. (See Fig. 2.) It was found that the CFM documented an abnormal pattern with the onset of hypoxia, hypotension, and hypothermia (11–13) as well as indicating the depth of anesthesia (12).

Results

In our experience an abnormality in GCEA can only be detected by comparing changes with respect to a baseline established in the same patient directly after induction of anesthesia.

The GCEA recordings were classified into four groups (13):

Group I, recordings essentially unchanged;
Group II, mild transient abnormalities (less than 4 minutes);
Group III, recordings showing severe or prolonged abnormalities, returning to normal;
Group IV, severe or prolonged abnormalities, no return to normal.

Of 38 patients operated on under normothermia or mild hypothermia, 35 were in Groups I and II, 2 were in Group III, and one was in Group IV. In 27 patients, during the entire operative procedure, the GCEA was without change (Fig. 2). In 7 (20%) of 35 patients during perfusion, GCEA decreased (more than 10 microvolts), regardless of calculated pump flow and normal arterial blood gases. Neo-Synephrine drip into pump promptly increased MAP and GCEA returned to preperfusion level (Fig. 3).

Of the 124 patients with normal GCEA after induction of anesthesia, all were undergoing hypothermic cardiopulmonary bypass (Figs. 4, 5) and were classified as Group III. After rewarming, the GCEA of 120 patients returned to prehypothermic levels (measured in microvolts). All emerged from anesthesia neurologically intact. The GCEA of two patients leaving the operating room was lower by more than 10 microvolts than their preoperative GCEA levels, but both had an uneventful recovery. Two other patients (both underwent coronary artery bypass grafts) revealed significant low cardiac output syndrome with poor left ventricular function. Neither responded to pharmacological and intra-aortic balloon pump support and both died. Eight patients (grouped as "Other" in Table I) were in cardiogenic shock, with significant low GCEA, prior to open-heart surgery. Surgery for these patients was carried out under deep hypothermia (20–22°C midesophageal temperatures). Three had improved GCEA, compared to preoperative levels; two of these patients recovered and one died 24

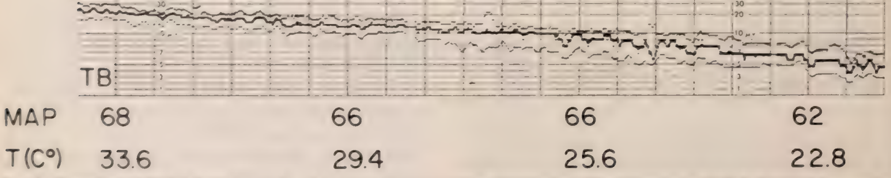

FIG. 4. Recording of GCEA during open heart surgery. Demonstration of influence of hypothermia on GCEA, which is decreasing with temperature. Key: TB, total bypass; MAP, mean arterial blood pressure; T(C°), midesophageal temperatures.

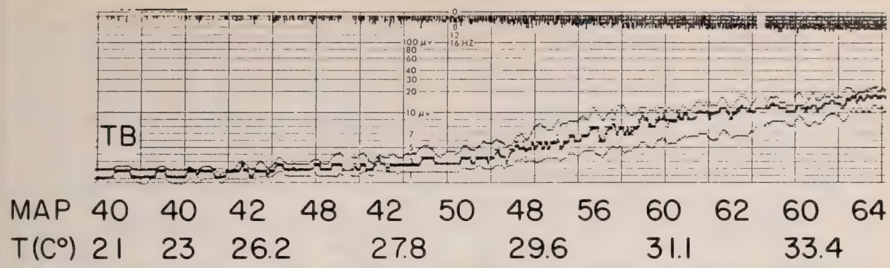

FIG. 5. Recording of GCEA during open-heart surgery. Return of GCEA to prehypothermic levels with correlation of the rewarming. Key: TB, total bypass.

hours after surgery. Five had the same low GCEA after rewarming; of these, two recovered and were discharged from the hospital without neurological sequelae, and three died during the postoperative period.

Discussion

Inadequate cerebral perfusion is a well-recognized hazard of open-heart surgery (2–4, 13, 16, 17). Although CFM monitoring does not provide information concerning focal cerebral injury, early warning signs of dysfunction as indicated by changes in GCEA allow for a more immediate investigation of the cause (Fig. 6). One of the most critical periods during open-heart surgery is the onset of cardiopulmonary bypass. Cerebral circulation during this time is exposed to several changes: nonpulsatile flow; decrease in oxygen-carrying hemoglobin due to hemodilution; and decrease in mean arterial blood pressures.

The additional hazards of asymptomatic, unrecognized atherosclerotic changes in the carotid arteries or cerebral vasculature often imposes an added risk. The early recognition of untoward changes in the cerebral circulation during the onset of cardiopulmonary bypass is beneficial even if the exact cause is not immediately obvious. Changes in GCEA (decreased microvolts, corresponding with lowering of Hertz levels) during the onset of cardiopulmonary bypass in normothermic states allow for evaluation of the state of perfusion and correction of suboptimal conditions, such as

1. increasing perfusion flow.
2. use of vasoactive pharmacological agents to increase mean arterial pressure; this action may improve cerebral blood flow and return the GCEA to a level which was observed before cardiopulmonary bypass.
3. checking for hypoxia due to inadequate oxygenation (16).
4. repositioning of misplaced superior vena cava cannula (17).

Review of our data supports use of the CFM in optimizing perfusion (Fig. 2). Measuring the GCEA during the onset of bypass supplies additional information not available from the mean arterial blood pressure and flow rate. Moreover, several rare complications were recognized early because of changes in GCEA (10–17, 35).

During ideal open-heart surgery, there are no changes in GCEA throughout the entire operation. Using present techniques, the most influential factor is change in hypothermia. A decrease in GCEA is a response to deepening levels of hypothermia which is not predictable. In general there is a decrease of the GCEA starting at moderate hypothermia (midesophageal temperatures between 32°C and 28°C); with a core temperature below 25°C the GCEA approaches zero. In most cases this decrease is smooth; in others there are a series of epileptiform spikes in the GCEA. Hypothermic protection of the central nervous system is a well-accepted technique in open-heart surgery. Once the GCEA has reached zero level in response to hypothermia, renewal of electrical activity (spikes or increased level) before rewarming is begun may indicate suboptimal

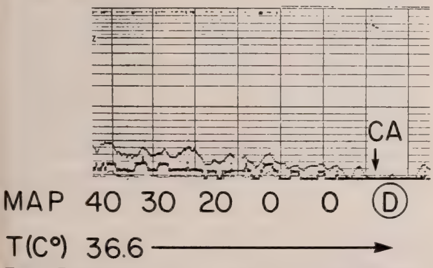

FIG. 6. Demonstration of one tracing from patients described in text. Patient's GCEA decreased to very low levels (4 microvolts) after cardiac arrest. Key: MAP, mean arterial blood pressure; T(C°), midesophageal temperatures; CA, cardiac arrest.

protection of the central nervous system and necessitate modification of the perfusion.

It must be stressed that prediction of the neurologic status of the patient postoperatively from changes in GCEA is not possible. Acute changes in hemodynamic function (cardiac output, major dysrhythmias, insufficient oxygenation) may cause transient or permanent dysfunction in the central nervous system within a few minutes or may have no noticeable effect.

Additionally, a CFM may be potentially useful in the operating room during elective hypotensive anesthetic techniques (orthopedic, plastic, vascular, neurosurgical) to alert the operative team of untoward neurologic response. In the intensive care unit, continuous monitoring of GCEA (18) will provide additional information about the progress of treatment in comatose patients after cardiac arrest, and in cases of brain trauma and different types of shock and resuscitation. This important area requires further careful clinical evaluation.

Evaluation of cerebral function with continuous monitoring of the GCEA in various clinical settings has enabled us to predict potential damage and, more important, apply therapeutic interventions to reverse the damaging neurological effects (19–22).

Summary

Continuous monitoring of global cerebral activity with the newly introduced cerebral function monitor (Critikon model 870) is a simple, useful method for early detection of cerebral changes. Used in 170 patients who underwent open-heart surgery, it has provided information helpful in prevention, detection, and early treatment of neurological dysfunction. Changes in global cerebral electrical activity during the onset of bypass may allow for optimized perfusion (increase in flow rate or the use of vasoactive pharmacological agent). We believe that although the cerebral function monitor is limited in that it provides no information on degree or location of injury, it does provide knowledge that there is something amiss with cerebral perfusion requiring immediate attention and further careful evaluation and treatment. In daily practice the CFM can supply first-line diagnostic information. When cerebral dysfunction is suspected, further evaluation should be undertaken and protective therapeutic steps initiated.

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Submitted for publication August 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Ventricular Arrhythmia Induced by Vasopressin: Torsade de Pointes Related to Vasopressin-Induced Bradycardia

EDWARD EDEN, M.D., ALVIN TEIRSTEIN, M.D., AND ISAAC WIENER, M.D.

Ventricular tachycardia secondary to intravenous vasopressin therapy has been described by Kelly (1). We report a second case which allows important observations on the mechanism of arrhythmia induction and the appropriate therapy.

Case Report

A 37-year-old white man was admitted to The Mount Sinai Hospital with hematemesis. In 1978, liver biopsy demonstrated alcoholic hepatitis; subsequently the patient had been hospitalized on many occasions for hemorrhage from esophageal varices which had been treated successfully with vasopression infusion and when necessary a Sengsterken Blakemore tube. There was no history of hypertension, congestive heart failure, or ischemic heart disease. On past admissions, periods of bradycardia with ventricular premature beats had been noted during vasopressin therapy. The patient was undergoing a course of variceal sclerosis therapy when the current episode of bleeding occurred.

His pulse rate was 80/min. and regular blood pressure 170/102 mm Hg lying, 145/82 mm Hg standing. He was jaundiced and pale with palmar erythema and spider nevi. A II/VI systolic ejection murmur was heard best at the left sternal border and transmitted to the apex. There were no signs of congestive heart failure.

ECG revealed sinus rhythm at 80/min with a QT interval of 0.42 seconds ($N < 0.35$) and nonspecific ST-T changes. Chest roentgenogram was normal. Hemoglobin concentration was 12.2 gm/dl. Serum electrolyte concentrations were sodium, 137 mEq/l; potassium, 3.5 mEq/l; chloride, 110 mEq/l; carbon dioxide, 27 mEq/l; magnesium, 1.7 mg%; and calcium, 8.7 mg%. Total bilirubin was 3.1 mg% and the prothrombin time was 13.8 sec (control 11.8).

Nasogastric aspirate yielded fresh blood which did not clear with ice saline lavage. The patient was transfused with packed cells treated with intravenous vasopressin infusion at a rate of 20 U/hour, gradually increasing to 30 U/hour. Emergency gastroscopy showed brisk eosphageal bleeding from varices.

During infusion, periods of sinus bradycardia developed. Runs of multiform premature ventricular contractions and periods of ventricular bigeminy became more frequent. There was no chest pain. The vasopressin was gradually tapered but approximately 46 hours after the start of vasopressin, the infusion rate now being 12 U/hr, asymptomatic ventricular tachycardia of the Torsade de Pointes type developed. (Figure 1, Panels A and B.) Marked QT prolongation (>0.6 sec) was noted immediately before the onset of the arrhythmia. Immediately after spontaneous termination, sinus rate was 56/min with a QT interval of 0.52 sec. Electrolytes were normal at this time, with potassium at 4.7 mEq/l (Figure 1, Panel C). The patient was treated with 0.6 mg of IV atropine and as the heart rate rose, ventricular ectopy diminished. Repeated atropine boluses were given to maintain heart rate above 70/min

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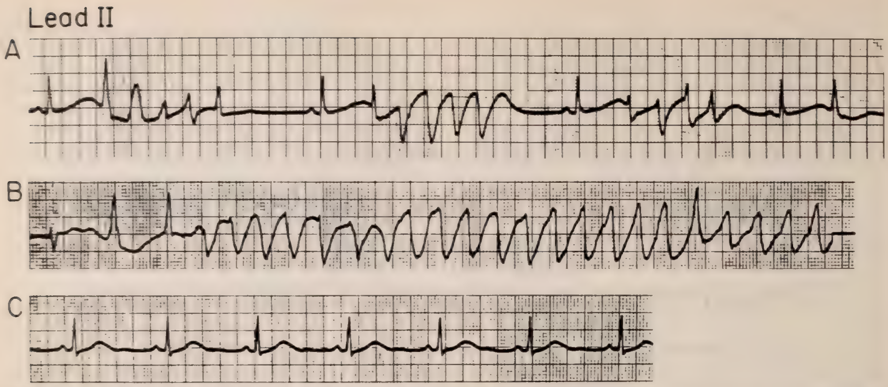

Fig. 1. Representative electrocardiogram. **Panel A:** Several short runs of polymorphous VT. Note the markedly prolonged QT interval on the sinus beats preceding the arrhythmias. **Panel B:** A longer run of ventricular tachycardia, demonstrating the Torsades de Pointes morphology. **Panel C:** A period of sinus bradycardia immediately following Panels A and B. Note the prolonged QTc (QT interval, .52 msec at heart rate 56 bpm).

and the vasopressin was rapidly reduced. After 24 hours an adequate rate was maintained without atropine. Repeated 12-lead electrocardiograms showed no acute changes and repeated estimations of cardiac enzymes were normal. A Holter monitor tracing off vasopressin showed occasional ventricular bigeminy and an M-mode echocardiogram was normal.

In anticipation of further hemorrhage requiring vasopressin therapy and to prevent further periods of sinus bradycardia, a permanent transvenous demand pacemaker programmed to a rate of 70/min was inserted. During a further upper gastrointestinal bleed, vasopressin at 25 U/Hour slowed the heart rate from an initial 95/min to a pacemaker rhythm.

Discussion

We have described a case of torsade de pointes related to a prolonged QT interval in the setting of sinus bradycardia secondary to intravenous vasopressin infusion. On admission, our patient had a minimally prolonged QT interval, with no history of malignant ventricular arrhythmias in the resting state. We postulate that vasopressin, by inducing sinus bradycardia, caused sufficient further prolongation of the QT interval to induce torsade de pointes.

In a report by Kelly et al (1), ventricular arrhythmias secondary to vasopressin were ascribed to the hemodynamic effects of vasopressin, including prolongation of pre-ejection period, reduction of cardiac output, and constriction of coronary arteries (2–5). It is of interest, however, in reviewing the report by Kelly, that QT interval was prolonged before pitressin (.38 sec for heart rate 93 beats per minute) and became more prolonged during the bradycardia induced by vasopressin (0.44 sec at 64 beats per minute). Bradycardia is a well-known effect of vasopressin (2, 3).

The causes of a prolonged QT interval in our patient are unknown (7). Electrolyte concentrations, including potassium and calcium, were normal. There was no recent alcohol intake and no evidence of cardiac ischemia during bradycardia. A case of cardiomyopathy with a prolonged QT interval and spontaneous ventricular tachycardia has been described (6) and although our patient's echocardiogram was normal, the possibility cannot be excluded. There is no clinical evidence that the patient's prolonged repolarization was of any significance except when exacerbated by vasopressin.

Antiarrhythmic agents that prolong the QT interval are contraindicated in such patients (7–8). These contraindicated agents include procainamide, quinidine, and disopyramide. Atropine and isoproterenol increase cardiac rate, decrease the dispersion of refractoriness in ventricular myocardium (9), and are recommended as acute treatment for torsade de pointes. Atrial or ventricular pacing achieves the same effect; both have been used effectively to prevent ventricular arrhythmias in the setting of a prolonged QT interval (8, 10).

We wish to draw attention to an entity of bradycardia and secondary QT prolongation during vasopressin infusion followed by torsade de pointes. This arrhythmia should be treated in the acute stage with atropine or isoproterenol, followed by possible use of a pacemaker.

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Submitted for publication May 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

The Value of Tomography in Diagnosing Infection of the Sternoclavicular Joint

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Abstract

The diagnosis of infectious sternoclavicular arthritis is often missed in the early stages. Five patients with this disease were diagnosed only after the development of erosive changes of the articular surface. Even then, the erosive changes and the periarticular soft-tissue masses could not be delineated without the aid of conventional and computed tomography. Tomography of the joint appears to be essential in making an early diagnosis of infection of the sternoclavicular joint.

In reviewing the literature, infection of the sternoclavicular joint appears to be relatively uncommon and occurs predominantly in drug addicts with gram-negative bacillary infections. This statement may be misleading. It is our experience that infection of the sternoclavicular joint can occur in otherwise healthy individuals, gram-positive cocci being the offending agent.

The sternoclavicular joint is a small synovial cavity formed by the medial end of the clavicle, the clavicular notch of the manubrium sterni, and the adjacent part of the first costal cartilage. The initial signs of infection are often insidious in origin and misdiagnosed. An elevated erythrocyte sedimentation rate and a normal white blood count are common. The joint is poorly visualized on routine radiographs, and tomograms are often necessary to establish the correct diagnosis. Because of the difficulty in establishing an early diagnosis, secondary osteomyelitis may arise.

Infection of the sternoclavicular joint is not commonly reported in the literature (1–3). Among the various bacterial organisms that may infect this joint, gram-negative bacilli in intravenous drug abusers have been implicated most commonly (4, 5).

This report details our experience with five patients who developed sternoclavicular joint infection and osteomyelitis of the adjacent bone. It is our experience that sternoclavicular joint infections may be more common than indicated in the literature, particularly in the non-drug-addict population.

Case Reports

Case 1. A 52-year-old white female was admitted to the hospital because of pain and swelling of the right side of the chest for five days. She had a history of rheumatic heart disease and had undergone mitral valve replacement five years before. On admission there was tenderness at the right sternoclavicular joint. Bone scan and gallium scan were positive in the region of the proximal right clavicle and first rib. Radiographic examination revealed a hazy area in the right upper lung field. Tomography and computerized tomography showed an extrapulmonary mass eroding the anterior part of the right sternoclavicular joint extending to the adjacent area of the right first rib (Figs. 1, 2). The erythrocyte sedimentation rate was 100 mm/hr, the white blood count was 10,600, and blood cultures were negative. Biopsy of the proximal clavicle revealed necrotic tissue and chronic inflammation. Cul-

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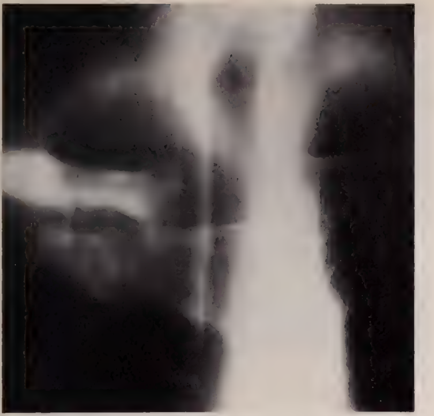

FIG. 1. **Case 1.** Tomography of the right sternoclavicular joint shows erosion of the sternoclavicular joint with involvement of the anterior part of the first rib.

tures were negative. The patient improved clinically on a month's course of intravenous oxacillin.

Case 2. A 74-year-old white male was admitted to the hospital with *Staphylococcus aureus* urosepsis. Two years previously he underwent orchiectomy, followed by steroid therapy and radiotherapy, for carcinoma of the prostate.

He was treated with oxacillin and responded well to the therapy. On the sixth day during therapy, he developed a cystic mass over the proximal left clavicle. A bone scan was positive in multiple foci, but a gallium scan was positive only at the area of the left sternoclavicular joint.

Radiological examination, including tomography and computerized tomography, revealed erosion of the left sternoclavicular joint (Figs. 3, 4). The patient improved and the mass resolved on continued oxacillin therapy.

Case 3. A 22-year-old white female developed chest pain and a pustular rash on the arms and palms six weeks prior to admission. The white blood count was 12,700, the erythrocyte sedimentation rate was 47 mm/hr, and the venereal disease research laboratory result was negative. She was afebrile and denied recent sexual exposure or drug abuse. Skin biopsy was consistent with psoriasis. She then developed hip pain and right shoulder and right sternoclavicular joint arthritis. Plain radiographs were normal but tomography of the sternoclavicular joint revealed erosive changes. Biopsy of the sternoclavicular joint showed chronic osteomyelitis. The bone biopsy and blood, cervical, oral, and anal cultures were negative. The patient has improved on antibiotics.

Case 4. A 47-year-old white female had had one month of pain in the right sternoclavicular joint. She had no fever and was otherwise well. The

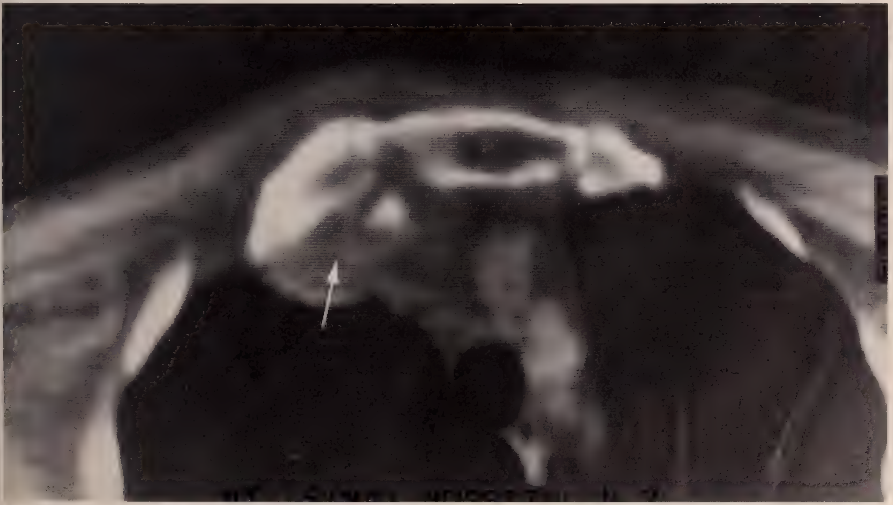

FIG. 2. **Case 1.** Computerized tomography shows, in addition to the erosion of the sternoclavicular joint, concomittant soft tissue mass (arrow).

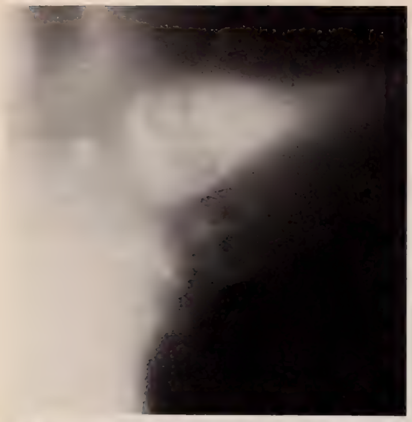

FIG. 3. **Case 2.** Tomography of the left sternoclavicular joint shows destruction of the inner end of the left clavicle.

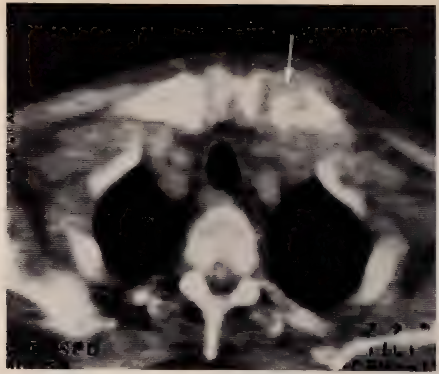

FIG. 4. **Case 2.** Computerized tomography reveals erosion of the anterosuperior aspect of the inner end of the left clavicle. The articular surface of the manubrium is indistinct and a concomittant soft tissue mass is noted (arrow).

white blood count was 7700 and the erythrocyte sedimentation rate was 7 mm/hr. Plain radiographs of the sternoclavicular joint were normal but tomography revealed erosive changes. Biopsy of the joint grew out *Staphylococcus epidermidis.* The infection resolved with six weeks of intravenous oxacillin.

Case 5. A 25-year-old Hispanic male developed an infection of the left sternoclavicular joint insidiously over one month. He had a history of drug abuse but definitely no use of intravenous drugs in the two years prior to hospitalization. Routine radiographs were normal but tomography revealed erosive changes. Aspiration of the joint grew out *Staphylococcus aureus.* The infection resolved with intravenous antibiotics.

Results

Five patients with symptoms referable to the sternoclavicular joint were evaluated with routine radiographs, tomography, and computerized tomography (Table 1). No intravenous drug abuse, diabetes mellitus, malignancy, chemotherapy, or rheumatoid arthritis could be detected in four of these patients. The fifth patient had carcinoma of the prostate.

The patients' ages ranged from 22 to 74 years. There were three females and two males. The right sternoclavicular joint was affected in three patients; the left joint was affected in another two. Systemic urosepsis was found in one patient.

Since routine radiographs did not reveal pathology of the sternoclavicular joint, tomography was essential in confirming the diagnosis in all cases. Computed tomography was helpful in Cases 1 and 2 in outlining the concomittant soft tissue mass (Figs. 1–4). The diagnosis was confirmed in all patients by aspiration or biopsy of the joint.

The cultures grew *Staphylococcus aureus* in two

TABLE I

Clinical and Radiological Data on Five Patients with Sternoclavicular Joint Infection

Age/ Sex	Clinical Symptoms	Joint Involvement	Bone/ Gallium Scan		X-ray			Aspiration Biopsy:		
					Routine	Tomo	CT	Inflammation	Culture	Results
52/F	right anterior chest wall pain	right sternoclavicular and 1st sternocostal joint	+	+	+	+	+	chronic	neg.	improved
74/M	left upper chest cystic mass	left sternoclavicle	+	+		+	+	acute	*S. aureus*	improved
22/F	swelling of right parasternal area	right sternoclavicle	+	+	–	+	+	chronic	neg.	improved
47/F	pain right upper chest	right sternoclavicle	none	none	–	+	none	chronic	*S. epidermidis*	improved
25/M	left shoulder pain	left sternoclavicle	none	none	–	+	+	acute	*S. aureus*	improved

cases and *Staphylococcus epidermidis* in another. The cultures were negative in the remaining two. In three patients who had bone biopsies the histologic sections showed acute or chronic inflammation.

Discussion

The sternoclavicular joint is known to be affected by systemic disorders such as rheumatoid arthritis, hyperparathyroidism, psoriatic arthritis, ankylosing spondylitis, and pseudogout. However, bacterial infection of this joint is considered rare.

Chartier reviewed 77 cases of septic arthritis from the Mayo Clinic during a period extending from 1939 to 1957 and found only one case affecting the sternoclavicular joint (3). In another large series, Goldenberg described acute infectious arthritis in 76 joints in 59 patients, and failed to find any involving the sternoclavicular joint (2). Masi and Eisenstein also failed to discover involvement of the sternoclavicular joint in 84 patients with 219 joints infected with *Neisseria gonococcus* (6).

Infectious arthritis of the sternoclavicular joint is frequently associated with an underlying predisposition to infection, for example, intravenous drug abuse, diabetes mellitus, malignancy, chemotherapy, and rheumatoid arthritis (7). Bayer et al reported eight patients with sternoclavicular joint pyarthrosis due to gram-negative bacilli (5), seven of whom were long-term intravenous drug abusers. In another recent review of sternoclavicular joint arthritis in which most of the patients were drug abusers, Yood and Goldenberg noted that certain gram-negative bacilli, particularly *Pseudomonas,* had a predilection for the sternoclavicular joint (4). No gram-negative organisms were cultured in our patients.

The onset of the clinical symptoms in sternoclavicular joint infections is usually insidious as opposed to other joints when involved with septic arthritis. The patients most often have anterior chest pain with restricted motion of the ipsilateral shoulder and arm. Fever is absent or low grade, and the white blood count and erythrocyte sedimentation rate are often normal. Four of our five cases fit this pattern and one had urosepsis. The four patients were otherwise well with no evidence of underlying infection. Osteomyelitis was present at the time these patients sought medical attention.

Because of the hidden location of the sternoclavicular joint, routine radiographs of the chest and even special oblique views of the sternoclavicular joint are usually inadequate to visualize the sternoclavicular joint in many disease processes (8). Conventional tomography and, recently, computerized tomography have been found useful to demonstrate the lesion properly (9). In our study, tomography was valuable in making the diagnosis of infection in all five cases. While conventional tomograms may demonstrate the bony erosions, concomittant intrathoracic or extrathoracic extension of a soft tissue mass can be visualized only by computerized tomography (Figs. 1–4). The pathogenesis of sternoclavicular joint infection is unclear. Localized subclinical osteoarthritis of the sternoclavicular joint is known to occur in the early twenties, and it is conceivable that these degenerative changes may be a predisposing factor for the infection (10).

In our five patients, the diagnosis of infectious sternoclavicular joint arthritis was unclear until appropriate radiologic examination with computerized tomography or tomograms revealed the pathology. Aspiration or biopsy of the sternoclavicular joint confirmed the diagnosis in all patients. All of our patients had osteomyelitis and the question may arise whether the osteomyelitis occurred before or after the joint infection. More work is necessary to study and better understand this process, although secondary osteomyelitis as a late complication of the joint infection may be anticipated.

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Submitted for publication May 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Splenectomy for Thrombotic Thrombocytopenic Purpura

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Abstract

A retrospective analysis of eleven patients with documented thrombotic thrombocytopenic purpura treated at The Mount Sinai Hospital from 1967 to 1979 is presented. Ten patients demonstrated an acute form of the disease, whereas one patient had chronic thrombotic thrombocytopenic purpura. All patients demonstrated microangiopathic anemia, renal dysfunction and thrombocytopenia. Ten patients had fever and neurologic symptoms. Preoperative management consisted of high-dose intravenous steroids in all patients. Eight patients received Dextran 70, and three patients dipyridamole and aspirin. Splenectomy was performed on all patients. Of the nine patients treated with steroids, platelet deaggregators, and splenectomy, six survived (66%). All survivors were off medication and well in follow-up performed from two to twelve years after splenectomy. Initial platelet counts below 25,0000/mm^3, age above 40, or any elevation of total serum bilirubin adversely affected survival in this series.

Thrombotic thrombocytopenic purpura is an uncommon, frequently fatal disease associated with a pentad of clinical findings: microangiopathic anemia, abnormal neurological signs, fever, thrombocytopenia, and renal dysfunction. The clinical entity was described by Moschcowitz in 1925 (1). The pathologic lesion of hyaline-like occlusion of arterioles and capillaries was elucidated by Baehr (2) and Craig and Gitlin (3). Recent evidence has demonstrated both IgM and complement-three (C-3) deposits in the vascular lesions of this disease, suggesting an immune basis (4, 5). However, the precise etiology of thrombotic thrombocytopenic purpura remains speculative.

This report reviews a 12-year surgical experience with this disease at The Mount Sinai Hospital, New York.

Materials

Eleven patients with thrombotic thrombocytopenic purpura underwent splenectomy from 1967 to 1979. Table I summarizes the characteristics of the patient population. It should be noted that the chronic form of this disease is very uncommon. This group included a distinct preponderance of Caucasians, but no clear-cut sex or age distribution.

Clinical and Laboratory Findings

All ten patients with acute thrombotic thrombocytopenic purpura had fever and neurologic dysfunction; the single chronic case had neither. The preoperative laboratory findings are summarized in Table II.

Microscopic study of the resected spleens demonstrated the classical vascular lesion in all specimens.

Operative Findings

The spleen was enlarged in four patients and normal size in seven. Three patients had accessory spleens. Six patients had the splenic bed

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TABLE I

Population Characteristics: 11 Patients with TTP

Age	17 to 61 years (mean, 35 years)
Sex	7 females, 4 males
Race	2 Negro, 9 Caucasian
Type of TTP	10 acute, 1 chronic

drained. Eight patients required blood transfusions during operation; the average transfusion was 850 cc per patient. All patients received platelet transfusions either promptly before the skin incision or immediately following splenectomy.

Early Postoperative Results

Of the 11 patients reviewed, five died in the early postoperative period. Table III lists the causes of death. These multiple causes of death are in keeping with the known multiorgan involvement of this entity.

Of the six surviving patients, five were below the age of 40, and five were female. Seven patients had an admission platelet count of 25,000/mm^3 or less. Five of these patients died in the early postoperative period. Four of the six survivors had an early and sustained increase in platelet count and hemoglobin concentration. These four patients also developed normal peripheral blood smears while in hospital. The remaining two survivors did not demonstrate a normal platelet count at time of discharge, and they continued to show microangiopathic changes in their peripheral blood smears. The hematuria resolved in all the survivors.

Five of the six survivors developed postoperative complications. One patient developed a left subphrenic abscess which required surgical drainage. Another developed *Klebsiella* bacteremia which responded to antibiotics. One patient developed left lower lobe pneumonia and acute renal failure which resolved with antibiotics and hemodialysis. No wound infections were noted. The average hospital stay for the survivors was 35 days.

TABLE II

Preoperative Laboratory Findings: 11 Patients with TTP

Schistocytes, Burr cells	positive (all)
Hemoglobin concentration	6 to 9.7 gm%
Platelet count	9,000 to 60,000/mm^3
Hematuria	3 gross, 8 microscopic
Total bilirubin	0.5–4.8 mgm%
Reticulocyte count	11.8% (average)
PT, PTT, fibrinogen	normal (all)
Direct & indirect Coombs	negative (all)
ANA, LE Prep	negative (all)

TABLE III

Causes of Early In-Hospital Postoperative Deaths Among 11 Patients with TTP

Cause of Death	No.
Acute myocardial infarction	2
Congestive heart failure & respiratory insufficiency	1
Progressive neurological deterioration	2
Total	5

Late Postoperative Results

The follow-up period ranges from two to twelve years, with a mean of six years. All six survivors are well and without any evidence of recurrent disease. None of the survivors have demonstrated evidence of collagen vascular disease. All patients have a normal blood smear, platelet count, hemoglobin concentration, reticulocyte count, and urine analysis, including the two patients who left the hospital with abnormal blood smears. All patients are off medication.

Discussion

The etiology of thrombotic thrombocytopenic purpura is unknown. A history of prior infection or drug reaction in patients with this syndrome is well documented (6–8). However, no specific microorganism or drug has been shown to cause the disease.

At present, the two most accepted theories evoke either a primary vasculopathy or some immune mechanism. Immunofluorescence and electron microscopic studies have demonstrated subendothelial lesions which appear to precede thrombosis (9). The presence of subintimal hyaline-like deposits in vessels without intraluminal thrombi supports a primary vasculopathy (10). Mant (4) and Weisenburger (5) have demonstrated the presence of IgM and C-3 deposits in the vascular lesions of thrombotic thrombocytopenic purpura, which suggests an abnormal immune mechanism. IgG has also been found in these lesions and in the platelets themselves (11). Low levels of serum C-3 also have been documented (12).

The diagnosis is suspected on the basis of the clinical picture and the characteristic peripheral blood smear. It is confirmed by the typical histological lesion of hyalinelike near-occlusion of the small vessels in multiple organs. A previous review has demonstrated the diffuse nature of the vascular lesions in this disease, including involvement of the myocardium, kidney, lung, brain, pancreas and intestine (13). This observation is supported by our own experience, in that the mode of death in our postoperative patients shows multiorgan failure, even though none had intrinsic cardiac, pulmonary, renal or central nervous system disorders prior to the development of thrombotic thrombocytopenic purpura.

Many therapeutic modalities have been used in the treatment of thrombotic thrombocytopenic purpura with varying degrees of success. Steroids, splenectomy, platelet deaggregators, heparin, exchange transfusions, plasmapheresis and hemodialysis, either alone or in combination, have been tried (14–23). Because of the relative rarity of this disease and the lack of any prospective, randomized clinical trials, the most effective treatment is unknown.

There is evidence that heparin therapy is not warranted unless unequivocal disseminated intravascular coagulation is present (23). Bukowski's report on the use of exchange transfusion seems promising (17), but other reports are contradictory (21, 24). Bukowski et al reported two patients surviving after intensive plasmapheresis without splenectomy (18). The basis of this treatment presupposes an underlying immune etiology. Because removal of immune complexes by plasmapheresis in other immune diseases has been of benefit, continued study of this therapy is justified (24, 26).

In recent years at our institution, therapy has consisted of high-dose intravenous steroids and platelet deaggregators. We have used either Dextran 70 alone or in conjunction with aspirin or dypyridamole. Urgent splenectomy is undertaken for those with progressive neurological dysfunction, lack of platelet response, or regression after initial improvement. We have not been able to identify a single patient in our institution with a confirmed diagnosis of acute thrombotic thrombocytopenic purpura who did not have a splenectomy within 24 hours after admission.

Of the nine patients treated with the above regimen, six survived. The two other patients who died were treated with high-dose intravenous steroids and splenectomy only. We were able to identify three unfavorable prognostic factors in this study: age, initial platelet count, and total serum bilirubin. Of the six patients 40 years or older, only one survived. Of the seven patients presenting with platelet counts below 25,000/mm^3, five died. Seven patients had total bilirubin levels above 2 mg%. Five of these patients died.

Other factors studied, including race, sex, neurological status, temperature, preoperative hemoglobin, white blood cell count, blood urea nitrogen, peripheral blood smear, reticulocyte count, urine analysis, choice of operative incision, use of drains, size of spleen, presence of accessory spleens, and amount of blood and platelet transfusion, did not affect survival in this series.

The long-term follow-up is remarkable in that none of the patients have developed signs of chronic thrombotic thrombocytopenic purpura. None have manifested systemic lupus or other collagen vascular disease, despite the 10%–20% incidence reported in the literature (25), and none show helmet cells in their peripheral blood smears.

Summary

Eleven patients with proven thrombotic thrombocytopenic purpura who had splenectomy are reported. Five died in the early postoperative period; six survived. All six survivors have remained alive for prolonged periods with apparently complete regression of the disease. The only preoperative findings of unfavorable prognostic significance in this series are age above 40, platelet count less than 25,000/mm^3, and elevated total bilirubin.

The presence of accessory spleens, use of drains, amount of platelet transfusion, race, sex, hemoglobin concentration, white blood cell count, blood urea nitrogen, blood smear, hematuria, reticulocyte count, neurological dysfunction, and fever did not appear to affect prognosis or complication rate.

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Submitted for publication April 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Adjustment to Ileostomy

Albert S. Lyons, M.D.

Social and economic adjustment to ileostomy has been a significant factor in determining *when* the operation is performed, *what* is done at operation, and *how* it is done.

In earlier years, the specter of a continually discharging stoma, inadequately managed by an unsightly appliance which only poorly controlled odor and contents, prompted physicians, surgeons, and patients to withhold operative treatment until the disease was an immediate threat to life or the patient was all but destroyed physically, socially, and emotionally. Furthermore, at operation, surgeons often embraced procedures which gave even the remotest chance of saving the rectum, rather than condemn the patient to what was perceived as a life of horror. The general lack of adjustment was the key factor. In recent decades, now that ileostomy has become more acceptable, the very technical details of fashioning the stoma have also been dictated, in substantial measure, by the experiences of ileostomates and their helpers, who have learned to evaluate the anatomically optimal properties of a stoma.

The proper management of an ileostomy therefore depends on a well-constructed stoma, a satisfactory, accurately fitted appliance, and psychological acceptance.

The Stoma

All too often, operators may show too little concern for what happens after the operation and make flush stomas or position them in undesirable spots. Generally speaking, the factors which should be addressed during the fashioning of an ideal stoma are:

1. Placement of the stoma, which should be chosen *before* operation.
2. Stab wound shape and size.
3. Abdominal wall opening.
4. Transaction of the ileum in relation to mesentery.
5. Antiprolapse reinforcing sutures.
6. Mucosal eversion.
7. Length of stoma.
8. Skin sutures.
9. Skin protection, which should be applied in the operating room.

All of these are significant, but virtually all problems posed by ileostomies can be mechanically solved if two particularly essential requirements of these nine are fulfilled: a satisfactory location on the abdomen, and adequate projection of the spout above the skin. Even when these two requirements are not satisfied, one may still get around the difficulties but the path can be devious and trying. A too-flat stoma, or one badly placed, can lead to distressing skin maceration through leakage around the faceplate of the appliance (Figs. 1–4). An ileostomy located too close to the anterior superior spine or in the midst of a wide scar or open wound can also create management problems.

The only other anatomical configuration which may be insurmountable and therefore may require revision is prolapse, a complication far less common at the present time than in the past but also usually dependent on the details of fashioning the stoma.

The Appliance

The older appliances were enough to discourage anyone on appearance alone and, when in use, repelled patient, family, and even nurses. Bulky, smelly, unreliable, they eventually led manufacturers to devise new constructions, employ more advanced substances, and achieve better adherence to the body contour.

The contemporary apparatuses are of varied materials, lie flat and circumspectly, emit no odor, and adhere to the skin by one means or another so that one glance by a preoperative patient at an adjusted, energetic, sometimes sexy ileostomate visitor usually is enough to convince the resistant.

The impetus which forced these innovations was provided by people who had had ileostomy performed and who banded together to form groups or ostomy societies, holding formal meetings and informal gatherings, organizing cadres to visit patients in hospitals and homes, and set-

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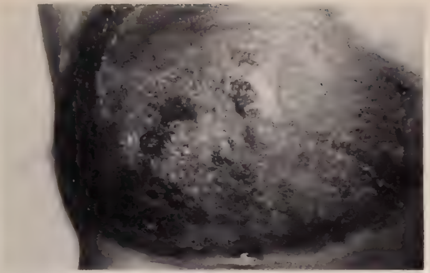

FIG. 1. Flat stoma with extensive skin maceration.

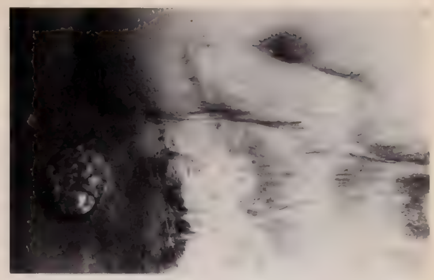

FIG. 3. Stoma buried in granulations, with obstructions but no skin problems because it projects above skin level.

ting up committees to evaluate the effectiveness of products sold or distributed to ostomates.

The first such reported club was formed at Mount Sinai Hospital in 1950, taking the name Q.T. after the two surgical wards at the hospital. Later a Boston group emerged and, in recognition of the Mount Sinai club's pioneering work, named itself Q.T. Boston. Meanwhile in Philadelphia a few postoperative patients with either ileostomy or colostomy were kept together tenuously by one dedicated, undaunted ileostomate. About the same time, all over the United States and Canada, small and later larger meetings of people with abdominal stomas began to be held, until finally the various groups convened into a loose federation of local societies, the United Ostomy Association. There are now about 500 chapters in the United States and Canada. Similar organizations abroad also formed and associated themselves in the International Ostomy Association (Fig. 5).

Of course, I am gratified and even proud to have been a starting spark in this now worldwide flame of activity, but in truth neither I nor any other member of the medical profession is entitled to more than chagrin that patients had to show us the way. We owe unbounded admiration for the devoted ostomates who led the frustrating struggle to convince lay people, physicians, and other professionals that their self-help direction was the effective path to social, economic, and emotional health.

The functions of ostomy societies are psychological, mechanical, and educational. The psycholog-

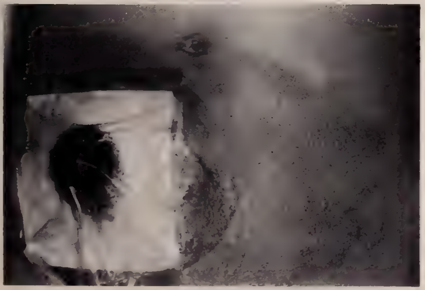

FIG. 2. Same stoma seven days after minor lifting above skin.

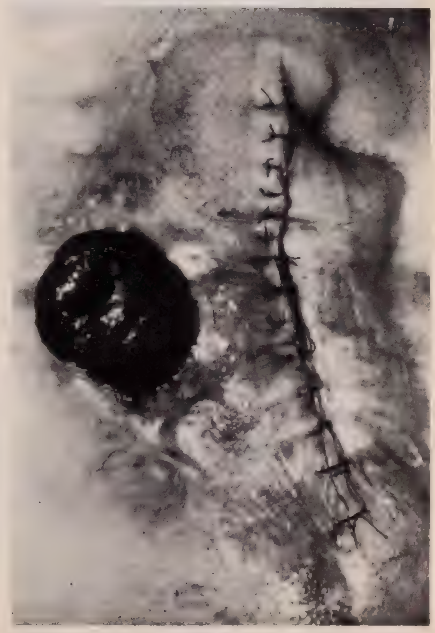

FIG. 4. Same patient immediately after major revision.

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FIG. 5. One of the earliest United Ostomy Association quarterly bulletins.

ical usefulness of these organizations is now generally recognized, so that one may be inclined to view the ostomy societies as entirely and solely devoted to promoting emotional support. But this—advantage though it may be—is not their only achievement. In earlier days, members of the visiting committees of these societies became such sophisticated technicians, experienced in the medical and mechanical implications of problems, that they were often the only knowledgeable instructors available to the postoperative patient. Moreover, at the formal general meetings of the ostomy societies every conceivable question related to stomas was addressed by guest lecturers or by the members themselves.

Of course, in more recent years, principally through the seminal work of Rupert Turnbull and Norman Gill of Cleveland, specially trained people—acting as enterostomal therapists—have become more numerous in many medical centers.

However, for a long time, the patient usually had nowhere to turn for information and help except to the local ostomy club. At first, at the conclusion of the meetings of the local Manhattan group at Mount Sinai, I would try to advise the members lining up to ask specific questions about themselves. The demands of time and numbers became too great, and so with the support of my surgical chief and the board of trustees, together with George Schreiber, Bernard Robinson, and Robert Turell, we were able to establish a special out-patient department section called the Intestinal Rehabilitation Clinic, the first such clinic of which I am aware devoted entirely to the evaluation and management of people with external stomas.

The third function of ostomy groups, education, is particularly observable in the activities of The United Ostomy Association's attempts to persuade employers, insurance companies, and the general public that rehabilitated ileostomates are healthy people living normal lives and capable of contributing fully to the economic and social well being of society.

Psychological Factors

As important to the patient's adjustment as are a well-fashioned stoma and a properly fitted appliance, a third underpinning is at least equally necessary—psychological acceptance. One may have an anatomically perfect ileostomy and an excellent, adherent appliance and yet fail to achieve rehabilitation. Here the ostomy societies have played an exceptionally beneficial part.

The salutary influence of an adjusted ostomate visitor on a preoperative candidate has already been mentioned; a similar postoperative elevation in mood is also often a striking result of a visit by an ostomate. Furthermore, the person newly initiated into the population of those with external openings from which fecal matter issues forth comes to realize that he or she is not alone. Close at hand is the potential support from many others who have experienced the same doubts and fears. After leaving the hospital, by attending the club meetings, the ostomate can continue to derive emotional strength through the camaraderie and positive attitudes shown by the members.

The psychological benefits resemble those seen in other group therapies: identification (with supportive allies active in the realities of living); expression (the chance to verbalize fears, resentments, and despair); sublimation (directing destructive energies into useful channels); integration (gathering one's disparate feelings into an organized personality).

Those whose psychologic mechanisms are not able to respond to these environmental influences may need the help of a psychiatrist. A patient may require the combined aid of both a psychiatrist and fellow ostomates. Indeed, all of the persons engaged in administering to the patient—surgeon, physician, psychiatrist, stomal therapist, nurse, and ostomy society members—play a role in guiding the patient into adjusted living. Each is needed and yet cannot fulfil the entire mission. This admonition may be especially applicable in the recent rivalry between the enterostomal therapists and local stoma clubs. But the surgeon too would do well to realize his continuing central importance, long after the operation and hospital stay. In my opinion, one should not perform an ileostomy on anyone whom one is not prepared to serve forever after. Everyone, professional or lay person, whether one realizes it or not, is actively engaged by word or deed in the psychological as well as the medical and mechanical treatment of the ostomate.

Present Status

At the present time ileostomates work in virtually every occupation—politics, truck-driving, dancing (Figs. 6, 7). They date, marry, or team up according to circumstances and their own personal attitudes, not the presence of a stoma. Breakups and divorces are rarely related to the ileostomy. Indeed, spouses and partners have often reported improvement in intimate relationships and sexuality after operation, compared with the status before ileostomy when the person was ill with colitis. The males have been potent and the females have become pregnant. Deliveries have been normal. When Caesarean sections have been necessary or complications have occurred, the reasons have been obstetrical. Neither surgical scarring nor the presence of a stoma has been the cause.

FIG. 7. Ostomate exotic dancer.

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NEW, DETACHABLE CHAPTER DIRECTORY IN THIS ISSUE

FIG. 6. Humor can lighten the burden.

Ileostomy has proved to be a price well worth paying for relief from colitis and therefore the prospect of an ileostomy should not lead to delay or avoidance of proper surgical treatment, provided it is accompanied by the continued commitment of surgeons, physicians, stomal therapists, and fellow ostomates to long-term management. At the same time, these spectacular rehabilitative achievements should not deter the search for curative medical therapy and innovations in operative procedures.

Submitted for publication June 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Hemangioleiomyosarcoma of the Pleura: A Case Report and Review of the Literature

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Abstract

A 21-year-old man had a large solitary hemangioleiomyosarcoma of the visceral pleura with coexisting benign hemangioleiomyomatous areas. The tumor was well encapsulated and easily removed surgically. It was characterized by the presence of vascular spaces, venous structures, and solid leiomyomatous and leiomyoblastomatous areas, each component exhibiting both benign and malignant features. Although two cases of primary pleural hemangioendothelial sarcoma have been described, we are not aware of another tumor with the complete features seen in our case.

The majority of localized (solitary) pleural tumors arise from the visceral pleura. They are characterized by the proliferation of mesenchymal spindle cells, and are usually classified as fibrous mesothelioma or submesothelial fibroma. They carry a good prognosis. However, because of diversified histological apperances and poor understanding of those tumors, more than 30 names, including fibroma, fibrosarcoma, myxosarcoma, fibrosarcoma myxomatoides, Ewing's tumor, endothelioma, chondroblastoma, angiofibroma, leiomyoma, and hemangiopericytoma, have been used in the literature. We recently had an opportunity to study an unusual localized tumor of the visceral pleura which occurred in a 21-year-old man. The tumor was composed of vascular spaces, distinct venous structures, and solid leiomyomatous and leiomyoblastomatous areas, each component exhibiting both benign and malignant histological features. No case with composite histological features of hemangioleiomyoma and hemangioleiomyosarcoma was included in the two recently published studies (1, 2) dealing with localized primary tumors of the pleura, totaling 58 cases, or in the two reviews (3, 4), one covering 152 cases and the other 360 cases, collected from the literature. We are aware of two cases of hemangioendothelial sarcoma, considered to be primary in the pleura; however, a myomatous or myosarcomatous component was not described in those cases (5, 6).

Case Report

A 21-year-old Hispanic man was admitted to The Mount Sinai Hospital with two chief complaints, severe right back pain and dyspnea for two weeks. He had been in good health until six months before, when he lost weight and developed a nonproductive cough. He denied fever and night sweats. He sought no medical care. The past medical history and family history were unremarkable. He did not smoke and had no known exposure to tuberculosis. Physical examination revealed a pale, chronically ill, young man with muscle wasting.

The blood pressure was 120/80 mm Hg; pulse 120; respirations 20; temperature 101.4°F; weight 139 lbs. The trachea was shifted to the left. The right chest was expanded with dullness to percussion and absence of breath sounds. The heart was markedly shifted to the left. The cardiac rhythm

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was regular and there were no murmurs. He had no palpable lymph nodes. The remainder of the physical examination was within normal limits. The urine was normal. The hemoglobin was 7.9 gm/dl; the hematocrit, 28%; the white-cell count, 8.100/mm^3, with 80% neutrophils, 13% lymphocytes, and 6% monocytes. The platelets were increased. The red blood cells were microcytic and hypochromic. The prothrombin time and partial thromboplastin time were normal. The chest radiogram (Fig. 1) revealed an opacified right thorax with mediastinum and heart shifted to the left. A tuberculin test was nonreactive.

Thoracentesis and pleural biopsy were performed on the day after admission. Only about 600 cc of serosanguineous fluid was obtained on multiple taps. The fluid contained total protein of 6.2 gm% and the lactic dehydrogenase determination was 1087 v/ml. The fluid was negative for AFB and malignant cells. The biopsy of the pleura was unrevealing. Two units of packed cells were transfused and thoracoscopy was performed. At thoracoscopy a huge gray encapsulated intrapleural mass was found. Because of engorged vessels on the surface of the mass, biopsy was not taken. A right thoracotomy was performed. A large solid and cystic tumor attached to the posterior aspect of the right lower lobe was resected. The right lung was pushed anteriorly and entrapped by nontumorous fibrous covering. Postoperatively, the patient had a prolonged air leak, but eventually the right lung was fully expanded. Before the patient was discharged, a metastatic workup, which included liver, brain, and bone scan, was negative.

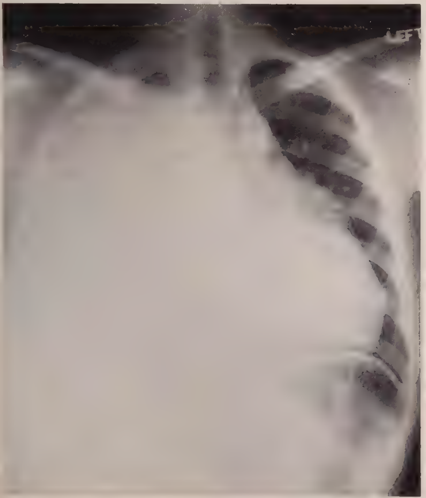

FIG. 1. PA. Chest radiogram showing an opacified right thorax with mediastinum and heart shifted to the left.

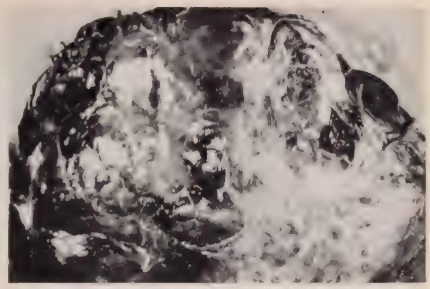

FIG. 2. Gross photograph showing the external surface of the tumor.

Pathology

The specimen consisted of a large, round, extremely hemorrhagic tumor mass measuring 27 × 17 × 15 cm and weighing 2800 gms (Fig. 2). It was covered by a thin dark purple capsule, mostly smooth and translucent, shaggy and torn in some areas. The external surface was nodular because of multiple cystic structures of varying sizes under the capsule. A small portion of lung measuring 3 × 2 × 1 cm was attached to one corner of the specimen. The visceral pleura appeared to be continuous with the capsule of the tumor. Section through the tumor mass revealed it to be mostly necrotic, particularly in the center (Fig. 3). There were many cystic spaces filled with clotted blood. The periphery of the tumor, where most of the viable tissue was found, exhibited a

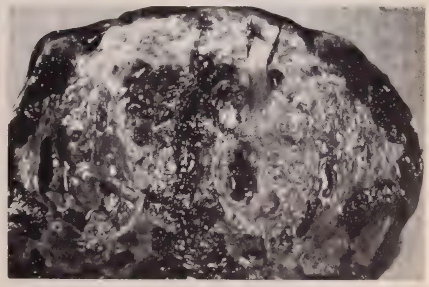

FIG. 3. Gross photograph showing the cut surface of the tumor.

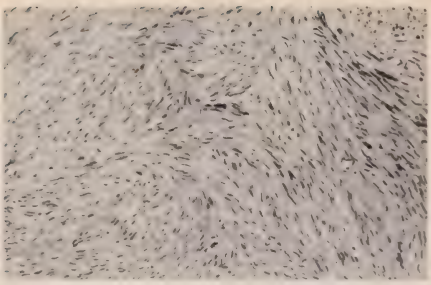

FIG. 4. Photomicrograph showing a leiomyomatous area composed of interlacing bundles of mature smooth muscle cells. (Hematoxylin and eosin, 40×)

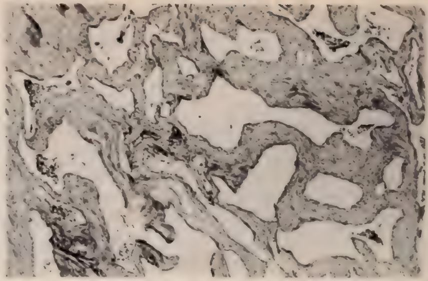

FIG. 6. Photomicrograph showing cavernous hemangiomatous area composed of anastomosing vascular channels lined by small flat endothelial cells. (Hematoxylin and eosin, 40×)

spongy texture of gray-purple hue interspersed with solid white areas. Spongy areas contained clotted or liquid blood. Solid areas ranged in consistency from soft to firm, and had a whorled appearance (Fig. 3).

Microscopically, the capsule consisted of dense fibrous tissue but mesothelial cells were not seen on the surface. The lung was not involved by the tumor. The tumor exhibited variegated appearances. Sections taken of the firm white solid areas showed typical features of leiomyoma, characterized by interlacing bundles of mature smooth muscle cells with bland elongated nuclei (Fig. 4). Occasionally, there were areas showing features of leiomyoblastoma, where tumor cells had an abundant clear cytoplasm (Fig. 5). No glycogen was demonstrated by PAS stain in the clear cytoplasm. The spongy gray-purple areas consisted of anastomosing cavernous vascular channels containing blood cells and occasional organizing thrombi. Those channels were lined by small flat endothelial cells and separated by septa made up of fibrous tissue and smooth muslce (Fig. 6). Solid myomatous and vascular components often merged (Fig. 7). Of interest was the presence of many thick-walled venous structures showing marked proliferation of smooth muscle cells in the walls. The appearance of these smooth muscle cells ranged from completely benign, to atypical, to frankly malignant (Figs. 8, 9 and 10). In certain areas, thick-walled venous structures anastomosed one to another (Fig. 10).

In addition to the benign leiomyomatous, leiomyoblastomatous, and cavernous hemangiomatous areas, there were frankly malignant areas which could be classified as leiomyosarcoma, malignant leiomyoblastoma, and hemangioendothelial sarcoma. Hemangioendothelial sarcomatous areas were characterized by irregular anastomosing vascular channels lined by plump pleomorphic endothelial cells with hyperchromatic nuclei. They exhibited occasional mitotic figures. Papillary buddings were constant features (Figs. 11 and 12). Thrombi of varying de-

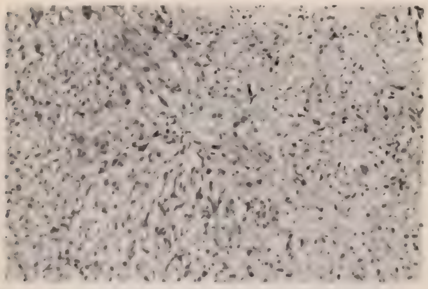

FIG. 5. Photomicrograph showing a leiomyoblastomatous area composed of interlacing bundles of clear cells with bland nuclei. (Hematoxylin and eosin, 40×)

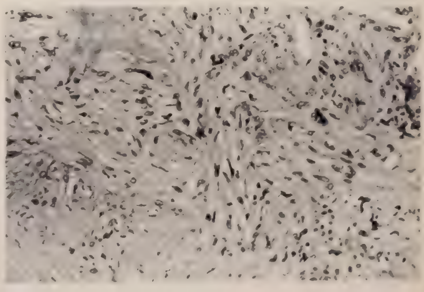

FIG. 7. Photomicrograph showing interlacing bundles of atypical smooth muscle cells, many of which exhibit clear cytoplasm. Mitotic figures are absent. A few vascular spaces are present in the right upper corner. (Hematoxylin and eosin, 40×)

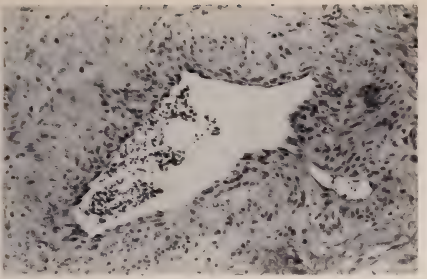

FIG. 8. Photomicrograph showing a thick-walled vessel with proliferation with smooth muscle cells in its wall. (Hematoxylin and eosin, 100×)

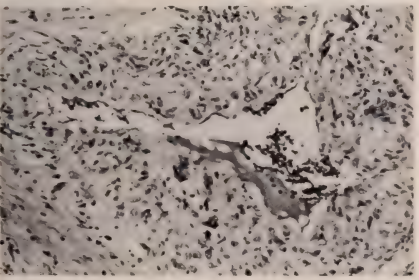

FIG. 9. Photomicrograph showing a thick-walled vessel with proliferating atypical smooth muscle cells in its wall. (Hematoxylin and eosin, 100×)

grees of organization were numerous. Solid sarcomatous areas were composed of haphazardly arranged, extremely pleomorphic tumor cells, either spindle-shaped or polygonal. Many cells had a clear cytoplasm. Multinucleated bizarre giant cells were seen scattered throughout the tumor. Mitotic figures, including abnormal forms, were abundant (Figs. 13 and 14).

Discussion

Since this tumor was covered by the continuation of the visceral pleura, and the parietal pleura and lung parenchyma were not involved, it is reasonable to assume that the tumor arose from the mesenchyme of the visceral pleura.

The majority of localized, solitary pleural tumors arise from the visceral pleura. They are characterized by the proliferation of mesenchymal spindle cells and are usually classified as fibrous mesothelioma or submesothelial fibroma. However, because of the diversification of histological appearance and poor understanding of these tumors, many names, such as fibroma, fibrosarcoma, myxosarcoma, fibrosarcoma myxomatoides, Ewing's tumor, endothelioma, chondroblastoma, angiofibroma, leiomyoma, and hemangiopericytoma, have been used in the literature. Some of those names certainly indicate a prominent vascularity of the tumors, yet none of these cases studied by Scharifker and Kaneko (1), Dalton et al (2), Shabana and Sayegh (3), or Briselli et al (4) exhibited truly diagnostic features of vascular tumors.

Since blood vessels are ubiquitous in the human body, vascular tumors, particularly the benign forms, are exceedingly common and occur in virtually every tissue and organ of the body. Vascular tumors are classified by their cellular constituents, possessing morphological and biological features of, or resemblance to, normal cellular components, mainly endothelial cells, smooth muscle, and pericytes.

Those vascular tumors composed of endothelial cells are called hemangioma, hemangioen-

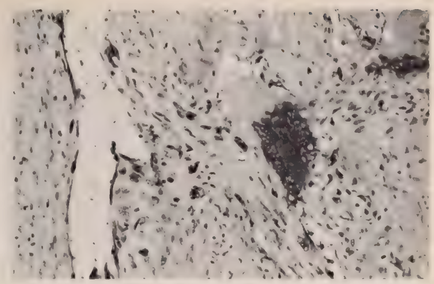

FIG. 10. Photomicrograph showing anastomosing vessels with markedly atypical smooth muscle cells. Endothelial cells are also atypical. (Hematoxylin and eosin, 100×)

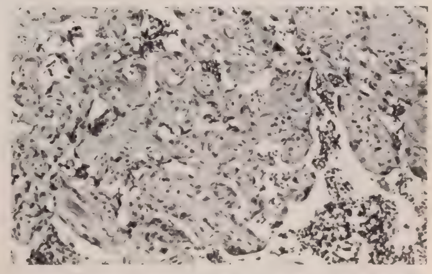

FIG. 11. Photomicrograph showing irregular anastomosing vascular channels lined by malignant endothelial cells. Many papillary buddings are present. (Hematoxylin and eosin, 100×)

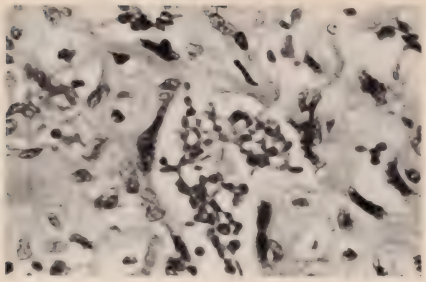

FIG. 12. Higher magnification of Figure 11 showing malignant endothelial cells with pleomorphic hyperchromatic nuclei. (Hematoxylin and eosin, 400×)

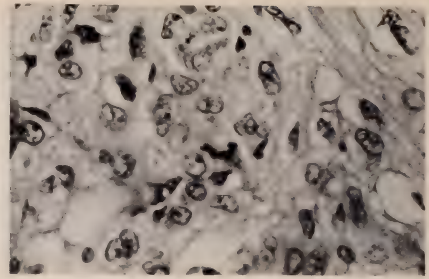

FIG. 14. Higher magnification of Figure 13 showing cellular details. Note many clear cells and an abnormal mitosis in the center. (Hematoxylin and eosin, 400×)

dothelioma, hemangiosarcoma, hemangioendothelial sarcoma, and so on. Pericytic proliferation is characteristic of hemangiopericytoma, glomus tumor, and Kaposi's sarcoma. Smooth muscle or endothelial cells are characteristic of vascular leiomyoma and hemangioleiomyoma. Of interest, however, is the absence in the literature of well-documented cases of hemangioleiomyosarcoma composed of both malignant endothelial and smooth muscle cells.

Despite the common occurrence of these vascular tumors on many parts of the body, the pleura, for unknown reasons, is rarely affected. Carter and Eggleston have not included any vascular tumor of the pleura in their monograph on lung tumors (7). We have found only two previously reported cases of hemangioendothelial sarcoma described as primary in the pleura (5, 6).

Although we cannot know exactly how long this patient harbored the tumor because he had been asymptomatic until six months before admission, the large size of the tumor and the presence of benign leiomyomatous, hemangiomatous, and hemangioleiomyomatous areas suggest that the tumor had been present for quite a long time. Some of the localized solitary tumors of the pleura are known to be present for many years without causing symptoms. The longest time interval between discovery of the tumor by routine chest x-ray and resection is 20 years, in Scharifker and Kaneko's (1) series. In these cases, the tumors tend to be larger.

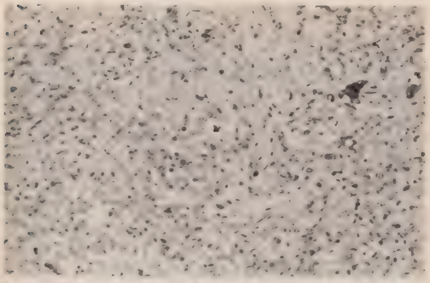

FIG. 13. Photomicrograph showing a solid sarcomatous area composed of pleomorphic smooth muscle cells with mitotic figures. (Hematoxylin and eosin, 100×)

Finally, the presence of intermediate atypical areas, as well as benign and frankly malignant components in one tumor, suggest that this tumor began as a benign composite hemangioleiomyoma, then underwent malignant transformation.

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Submitted for publication March 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Primary Lymphedema: Four Cases with Vessel and Node Findings

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Abstract

Primary lymphedema is thought to be due to a congenital or developmental defect in the lymphatic system with a delayed clinical onset in many cases because of collateral lymphatic flow. Abnormality of lymph vessels was originally considered to be solely responsible for the pathogenesis; however, nodal abnormalities have recently been described.

Four cases of primary lymphedema with various degrees of lymph vessel and node involvement are presented. The lymphographic appearances are discussed, nodal findings are emphasized, and the concept of primary lymph node abnormality is supported.

Primary lymphedema is an uncommon entity and is thought to be due to a congenital or developmental defect in the lymphatic system. It is to be distinguished from secondary lymphedema, in which a specific underlying disease process is always encountered. The major causes of secondary lymphedema are lymph node metastasis, with or without surgery or nodal radiation, and inflammatory diseases such as filariasis. Originally, abnormality of the lymphatic vessels was considered to be solely responsible for the pathogenesis of primary lymphedema. More recently, however, changes involving the draining lymph nodes are being described. We have recently studied four cases of primary lymphedema with various degrees of lymph vessel and node involvement. This report demonstrates these findings and further elucidates the possible pathogenesis of the entity.

Case Reports

Case 1. E.K. is a 58-year-old white male who presented with several months of painless swelling of the right lower extremity, unresponsive to diuretics, and several weeks of painless swelling of the groin and penis. On closer questioning, a history of intermittent minor episodes of right leg pain and swelling over many years was elicited. The patient had traveled extensively worldwide and had an episode of right thigh phlebitis twelve years previously. His further history was noncontributory. Physical examination revealed slight obesity, a 2/6 systolic ejection murmur, shotty inguinal adenopathy and swelling of the right lower extremity, greater distally than proximally. The scrotum was enlarged and edematous and the penile shaft was edematous distally. The remainder of the examination was unremarkable. Except for decreased potassium due to diuretic use, laboratory studies—including complete blood count, sedimentation rate, urinalysis, and stool guaiac—were within normal limits. Intravenous urogram showed a double collecting system on the right. Sonogram demonstrated no mass lesion in the abdomen or retroperitoneum. Liver-spleen scan revealed slight splenomegaly, and gallium scan was negative. Femoral venogram was normal and bipedal lymphography was performed (Fig. 1). On the right, there was extensive dermal backflow throughout the ankle and calf, with filling of dermal and minor superficial lymphatics and without visualization of major trunks. In the midthigh there was reconstitution of two major trunks (normal: 5 to 15) with extravasation of contrast material surrounding them. A third more medial trunk filled in a retrograde manner. These three trunks emptied into an abnormal group of inguinal nodes composed of one large poorly defined node with slight coarsening of

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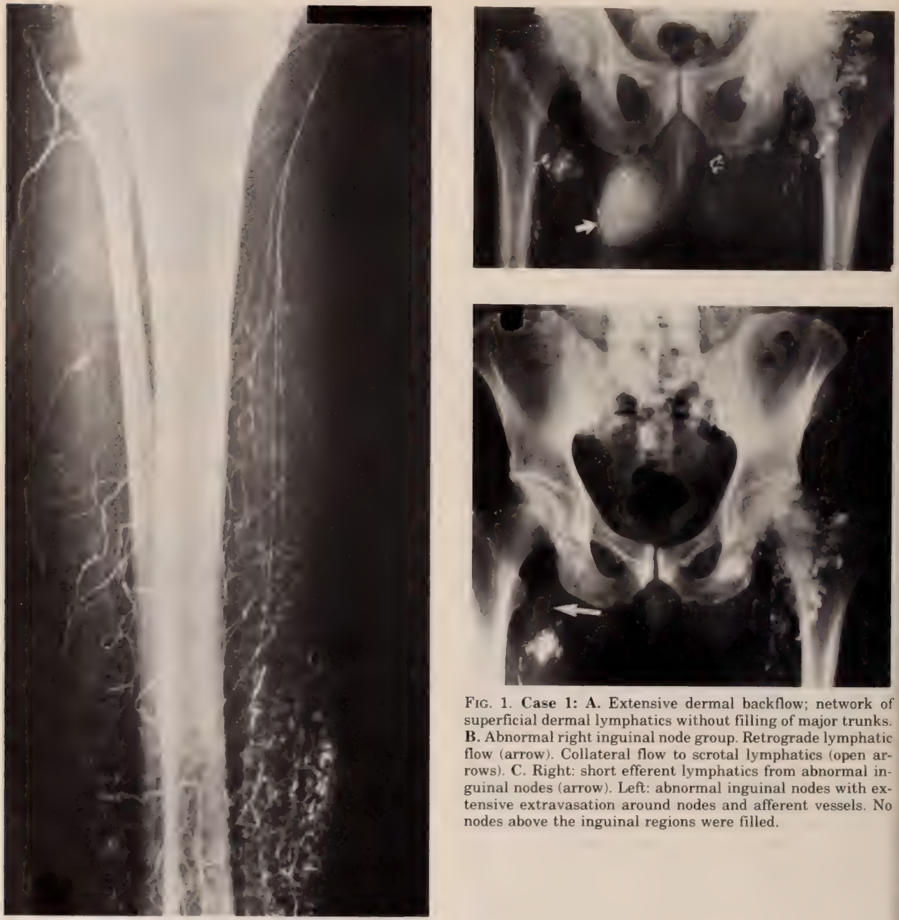

FIG. 1. **Case 1: A.** Extensive dermal backflow; network of superficial dermal lymphatics without filling of major trunks. **B.** Abnormal right inguinal node group. Retrograde lymphatic flow (arrow). Collateral flow to scrotal lymphatics (open arrows). **C.** Right: short efferent lymphatics from abnormal inguinal nodes (arrow). Left: abnormal inguinal nodes with extensive extravasation around nodes and afferent vessels. No nodes above the inguinal regions were filled.

the normal granular pattern and multiple smaller denser nodes. Several thin attenuated efferent lymphatic channels extended no more than three centimeters from the node group. In addition, collateral lymphatic flow to the scrotal area was demonstrated. No other right inguinal or iliac nodes were filled. On the left, multiple abnormal inguinal nodes were demonstrated; extensive extravasation surrounded them. Some nodes were large and poorly defined while others were small and dense. No lymph nodes were filled above the inguinal area, bilaterally, indicating complete obstruction at the inguinal level. No significant collateral pathways were demonstrated. Follow-up films for several days showed no interval change in lymphatic drainage or lymph node appearance. Percutaneous fine needle aspiration biopsy of the abnormal nodes yielded lymphatic tissue with no evidence of malignancy.

Case 2. J.S. is a 20-year-old white male who presented with 3 months of painless swelling of the left leg, beginning with left calf swelling following a skiing accident, and extending to involve the leg from groin to ankle. There were no accompanying symptoms of inflammation. His past history was noncontributory. Physical examination was within normal limits except for left lower extremity edema, greatest at the ankle and extending to the groin. Laboratory studies, intravenous urogram, and femoral venogram were normal.

Bipedal lymphogram (Fig. 2) revealed disorganized dermal lymphatics indicating dermal backflow in the left lower leg. From the medial side of the calf a single large, slightly irregular lymph channel extended proximally, completely bypassing the inguinal area, and entering an irregular group of left external iliac nodes. A single efferent vessel from these nodes was dilated and tortuous and did not fill past the sacrum. There was evidence of collateral lymphatic flow along the iliac wing to the iliac crest. None of the three left external iliac chains of nodes was complete. The nodes were small and dense, and there was extravasation around them. The left para-aortic nodes that were filled were small, dense, and slightly irregular.

On the right, the number and caliber of lymphatics in the leg were normal; however, some extravasation was noted in the lower leg. The inguinal nodes were perhaps slightly more numerous than normal. There was an extensive lymphatic network surrounding the external iliac nodes, with some dilated, tortuous, bypassing vessels. The lateral and middle chains of nodes were somewhat clumped and poorly defined, while the medial chain showed small dense nodes. The lower vena caval nodes were filled and were normal.

Case 3. J.L. is a 59-year-old black male who presented with several months of progressive right lower extremity swelling and swelling of his penis and scrotum. Leg swelling improved with elevation. His past medical history was unremarkable. Physical examination revealed a massively edematous right lower extremity with lesser edema on the left. Penile and scrotal edema were also noted. No adenopathy was present and the remainder of the examination was within normal limits. Intravenous urogram, barium enema, abdominal sonogram, and left leg venogram were normal. Pedal lymphography was unable to be performed on the right. On the left (Fig. 3), the clinically less involved limb, there was marked dermal backflow throughout the lower leg and thigh. Numerous small afferent vessels entered several abnormal clumps of inguinal nodes; collateral vessels were seen to extend laterally. On 72-hour films the inguinal nodes appeared dense and clumped with coarsening of the internal nodal architecture. No nodes above the inguinal area were filled. Excisional biopsy of two lymph nodes in the right inguinal region revealed fibrosis with no evidence of tumor.

Case 4. W.L. is a 16-year-old black male who complained of two weeks of swelling of the left lower leg and a localized lump below the left knee. The swelling increased with exercise and decreased markedly with elevation. There were no signs of inflammation. Past history revealed three episodes of pneumonia, gingivitis, and left inguinal hernia repair. An 18-year-old maternal cousin has a similar condition and a 13-year-old brother has Kartagener's syndrome. Physical examination revealed a small nontender, mobile, firm 5 × 3 cm mass anterior to the tibia just below the knee. There was mild pitting edema from there to the toes. Findings were otherwise nor-

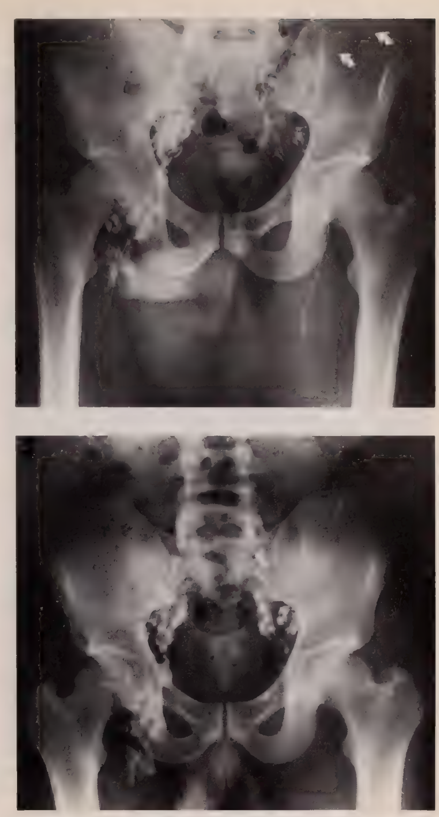

FIG. 2. **Case 2: A.** Solitary hypoplasia bypassing left inguinal nodes; superficial–deep lymphatic communication. Dilated and tortuous left common iliac vessel. Collateral lymphatic vessels (arrows). **B.** Left: small, rounded, dense external iliac nodes with some extravasation. Small collateral lymph nodes at iliac crest. Right: numerous inguinal and external iliac nodes with coarsening of internal architecture. Clumping of external iliac nodes.

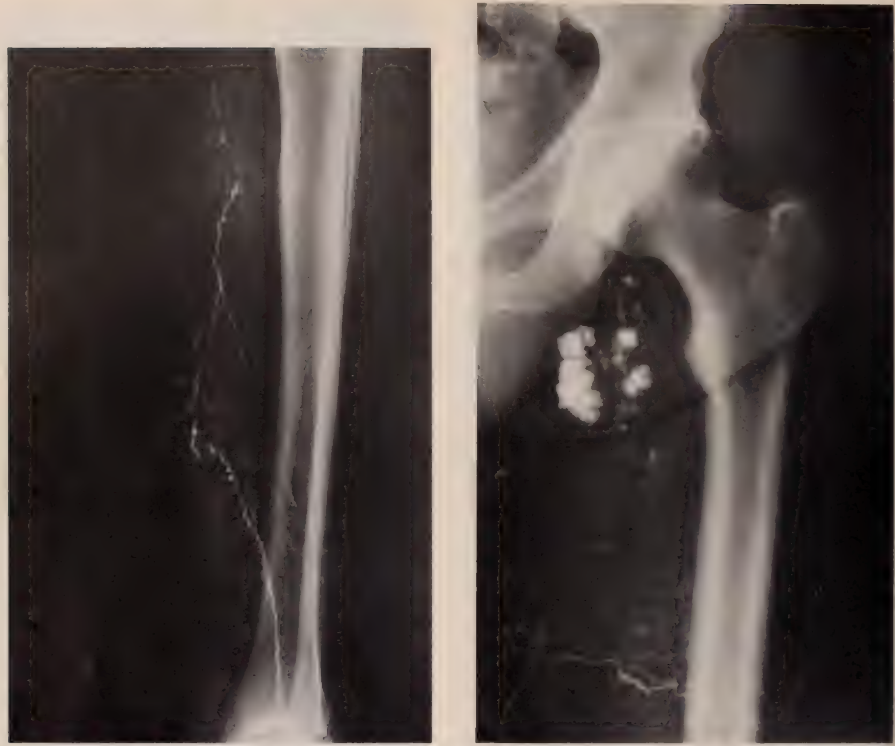

FIG. 3. Case 3. A. Extensive dermal backflow with dilated disorganized lymphatic vessels. B. Dense rounded inguinal nodes with coarsening of normal granular pattern. No nodes above the inguinal area were filled.

mal. Laboratory studies were normal. Doppler ultrasound examination revealed a normal venous system.

Bipedal lymphogram (Fig. 4) demonstrated a 10 cm area of dermal backflow at the midtibia on the left. From there a tortuous lymphatic extended to a globular collection of contrast material below the left knee anteriorly, representing a lymphocele. Four tortuous lymphatics extended to the inguinal area. On the right, a single dilated and tortuous lymphatic ran from the ankle to the inguinal area. Above the inguinal areas lymphatic vessels were within normal limits. In the mediastinum there was extensive reflux from the thoracic duct, filling large lymphatic channels to hilar and paratracheal lymph nodes. Supraclavicular lymph nodes were opacified bilaterally.

On 24-hour films inguinal, iliac, and para-aortic nodes were normal in size and shape, with perhaps slight coarsening of internal architecture. Paratracheal and hilar nodes were extensively opacified and appeared normal.

Discussion

A variety of classifications have been used to describe primary lymphedema. Kinmonth (1) in a study of 107 cases classified them according to age at onset and lymphographic appearance: lymphedema congenita present at birth, lymphedema praecox occurring in adolescents and young adults below age 35, and lymphedema tarda appearing above age 35. The majority of his cases belong to lymphedema praecox.

Primary lymphedema is best classified according to its lymphographic appearance. Hyerplastic, aplastic, and hypoplastic forms have been described. The hyperplastic form probably repre-

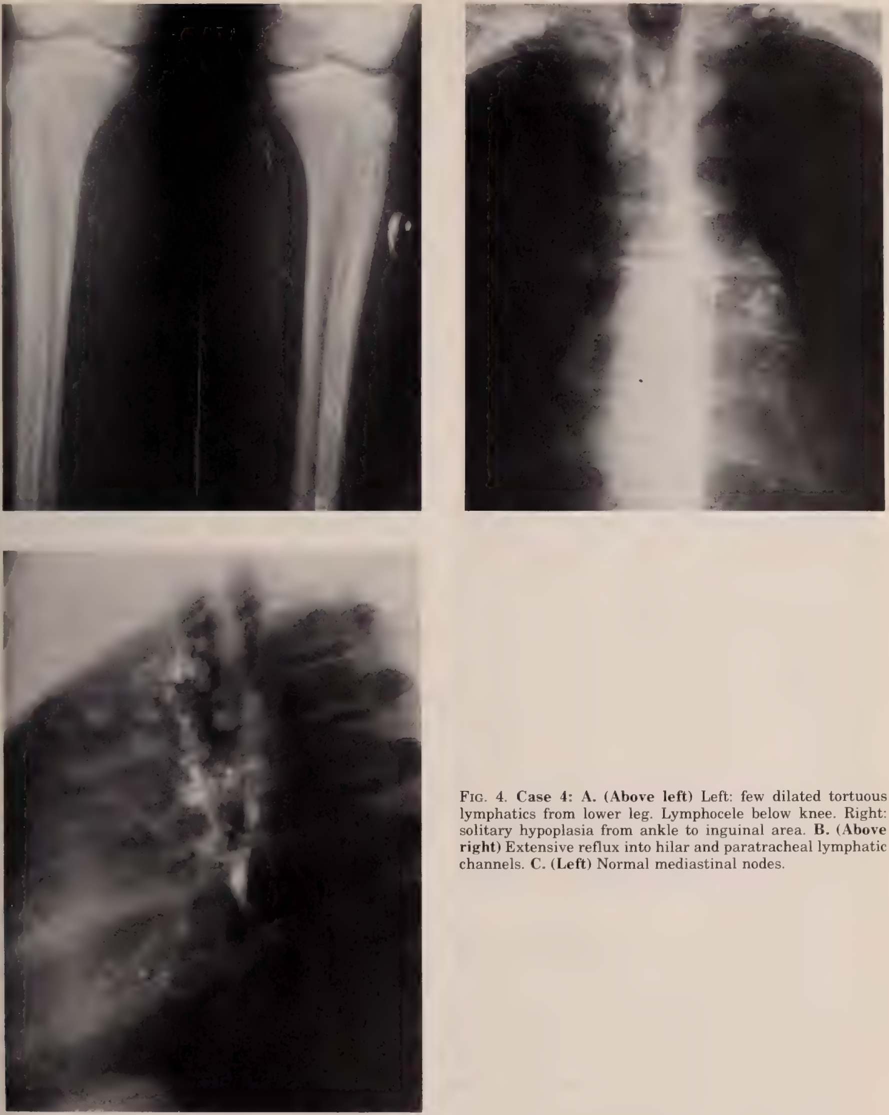

FIG. 4. **Case 4: A. (Above left)** Left: few dilated tortuous lymphatics from lower leg. Lymphocele below knee. Right: solitary hypoplasia from ankle to inguinal area. **B. (Above right)** Extensive reflux into hilar and paratracheal lymphatic channels. **C. (Left)** Normal mediastinal nodes.

sents a distinct entity and consists of an increase above normal in caliber or number of lymphatic channels. The channels may be varicose (megalymphatics) and are often associated with capillary angiomata, wine patches, or other congenital anomalies (2). In the aplastic form no demonstrable lymphatic vessels are encountered and lymphography is impossible. The hypoplastic form represents the majority of cases. It is seen predominantly in females and is associated with a family history in 25%. The lymphatic channels are smaller than normal in size and number and there is associated lymphographic evidence of obstruction. Obstruction is manifested by a delayed transit time, extensive extravasation of contrast material through vessel walls, dilated tortuous and beaded vessels, delayed clearing of contrast, or collateral lymphatic circulation. Collateral lymphatic circulation includes superficial–deep lymphatic communication, lymphovenous communication, and dermal backflow (1, 3). The latter is seen as an extensive, fine reticular pattern of lymphatic vessels due to the spread of contrast material through the superficial lymphatic system of the skin.

There are certain radiographic features which enable one to differentiate primary from secondary lymphedema. Both the clinical edema and lymphographic evidence of dermal backflow encountered in primary lymphedema commence distally in the extremity and progress proximally, whereas in secondary lymphedema the lymphographic findings are most striking immediately distal and adjacent to the site of obstruction (3). Analyzing the changes of the contralateral limb is also helpful in cases with unilateral edema. Abnormalities of lymph flow are often present in the clinically uninvolved extremity in patients with primary lymphedema, in contrast to secondary lymphedema in which the contralateral limb remains normal (4). Collateral lymphatic flow apparently is capable of compensating for the deficient lymphatic system in primary lymphedema until further deterioration of the system or functional overload secondary to inflammation, trauma, or hormonal imbalance results in clinically evident edema. This may explain the delayed clinical onset in lymphedema praecox and tarda.

Abnormalities within the lymph nodes have been demonstrated on lymphography in two large series (4, 5) and may be pathogenetically significant. They may represent the initial abnormality in the hypoplastic form of lymphedema. In a study of 55 cases (5), Kinmonth noted that 89% had involvement of both lymph nodes and vessels, 9% involved vessels only, and 2% involved nodes only. Since the flow of lymph from the periphery must pass through the regional nodes, obstruction at the nodal level could cause edema prior to any major involvement of the lymph vessels. Secondary changes in the lymph vessels may result from a back-pressure type of atrophy due to longstanding obstruction. Aplasia of regional nodes, suggested by complete bypass of these nodes by superficial–deep lymphatic communications, represents the greatest degree of involvement.

The basic change described in the hypoplastic form is a diminution in number and size of nodes. The nodes also appear more spherical or misshapen in configuration. The concentration of contrast within the nodes appears more dense and as a result the usual fine granular pattern within the nodes is lost. These changes need not affect all the nodes but may be nonuniform, affecting only some of a group of nodes. In addition, there may be extravasation around the involved nodal groups.

Our four cases belong to the hypoplastic form of lymphedema and demonstrate findings that support the concept of primary lymph node abnormality. The first three cases manifested a high degree of obstruction of the lymphatic system that appeared to originate at the lymph node level. Dermal backflow was extensive in the two cases without evidence of other collateral flow (Figs. 1 and 3). In a third case, backflow was less severe since superficial–deep communications helped bypass the obstruction (Fig. 2). The fourth case demonstrated bilateral lymph vessel hypoplasia and normal lymph nodes. However, slight coarsening of the normal granular pattern was observed (Fig. 4). A globular pretibial collection of contrast material was also noted that may represent a lymphocele, possibly secondary to unrecognized trauma. This may also have precipitated the clinical onset of lymphedema. Gough (4) described four cases of primary lymphedema with associated lymphangiomatous malformations, all presenting as groin masses.

Kinmonth (2), in discussing the amount of reflux into supraclavicular and upper and lower thoracic lymph nodes, noted that the percentage of lymphograms demonstrating reflux in primar lymphedema was equal to that in normals and in lymphoma. The refluxing nodes in primar lymphedema tended to be small, similar to thos encountered in the iliac chains. This feature wa not observed in our case, as the thoracic node opacified were normal in size and density (Fig. 4).

Although nodal abnormalities were demonstrated in our series also, additional changes wer seen, different from those previously described Many large nodes with decreased opacificatio and slight coarsening of internal architectur were noted. Some groups contained a larg number of small normally opacifying nodes; i others, larger nodes with normal opacificatio were clumped together. These abnormal change are difficult to evaluate at this time but may rep resent another part of the disease spectrum or early nodal changes. Follow-up lymphography would be helpful to elucidate the natural history of these nodes as well as the disease.

Acknowledgments

We thank Ms. Louisa Haigler for her secretarial assistance.

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Submitted for publication May 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Hydatid Cyst of the Pancreas: Case Report

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Hydatid disease is common in many parts of the world but it is a rare condition in Europe and the United States. The disease is due to two forms of the echinococcus tapeworm, Echinococcus granulosus and Echinococcus multilocularis, the former being the most common met in clinical practice. The most frequent site of arrest and development of the parasite is the liver (70%); next in frequency is the lung (20%). The pancreas is a very unusual location for primary hydatid disease, the total number of reported cases being less than 150. In Greece, where hydatid disease is common, lesions in the pancreas have been reported in 20 patients, representing 0.07% of all cases (1).

Case Report

The patient was a 60-year-old housemaid admitted to the hospital because of severe epigastric pain, fever, and jaundice. Ten days earlier she had severe epigastric pain and fever (39°C) with chills and vomiting. The next day she noticed her urine turning red and two days later observed a yellowish tint of conjunctivea and skin. The color of the feces became white. During the following days the pain subsided but fever, chills, and jaundice all became worse.

On physical examination, the liver was palpated slightly painful two fingers below the right costal margin. The gallbladder and the spleen were not palpated. The rest of the examination revealed no abnormalities. A chest and abdomen roentgenogram showed no abnormal findings. The hematocrit on admission was 44%; hemoglobin 14 gr%; leukocyte count 15,000; urea 0.55 gr%; blood glucose 1.19 gr%; bilirubin 6 mgr% (direct 4.8, indirect 1.2); SGOT 85; SLPT 120; alkaline phosphatase 68 (normal value <45); HBsAg negative; Casoni reaction negative; Weinberg reaction negative.

The patient was treated with intravenous fluids and she was given ampicillin (4 gr/24 h). On this regimen the general condition of the patient deteriorated. An emergent CT scan was performed. A large cystic mass, 8 × 7 × 8 cm, with well-defined borders and particularly thick wall (echinococcus?), was demonstrated in the head of the pancreas. Figure 1 shows the cystic mass from the point it comes into sight at the head of the pancreas (second film, upper right) to the hilus of the liver (bottom right). Dilatation of the intrahepatic biliary tree was also reported. From Figure 2, showing the mass after gastrographin in order to induce opacity of the duodenal loop, similar findings were reported.

Conclusion: Cystic mass of the pancreatic head.

Because the patient's general condition was deteriorating and because of the preoperative diagnosis of a cystic mass in the pancreas which was compressing the bile duct and resulting in cholangitis, an emergency laparotomy was decided upon.

Laparotomy

After opening the peritoneum, a cystic mass was found arising from the head of the pancreas. The liver was normal and no pathological findings were identified elsewhere. The cystic mass was displacing and adherent to the duodenal loop, the transverse colon, and the gall bladder. After cutting adhesions, the gall bladder appeared normal and the origin of the cystic mass from the pancreatic head was confirmed (Figure 3). Next, the cystic mass was entered by trocar and clear waterlike fluid obtained. Further exploration re-

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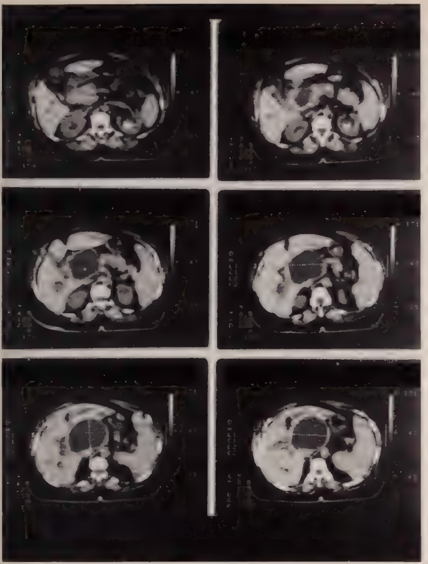


FIG. 1. The cystic mass.

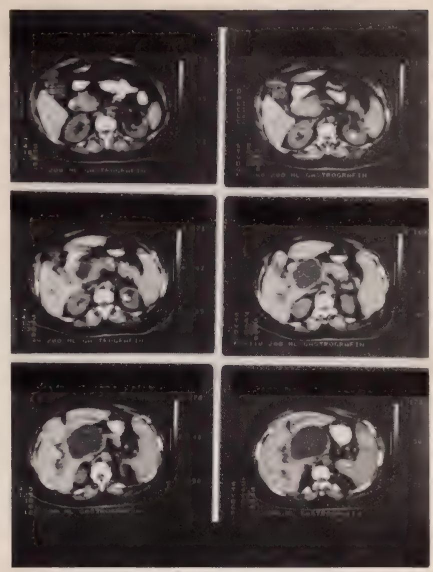


FIG. 2. The cystic mass after gastrographin.

vealed a large single-chambered echinococcus cyst containing many daughter cysts. The germinal layer was removed (Figure 4) and the cavity irrigated with hypertonic solution. After this an intravenous cholangiogram was obtained by injecting opaque medium through the gall bladder. Free passage of the dye through the common bile duct into the duodenum was observed. Opacification of common, left, and right hepatic ducts as well as of the intrahepatic biliary tree was not achieved (Figure 5). The common bile duct, however, was displaced to the right. After finger compression of the common bile duct, a second cholangiogram was performed with normal visualization of the intrahepatic biliary tree (Figure 6). The echinococcus cyst was drained externally and a cholecystostomy performed.

Postoperative Course

The patient's postoperative course was uneventful and her general condition improved. Repeated fistulograms of the residual pancreatic cavity revealed satisfactory reduction in its size. The drainage tube was then removed. Postoperative cholangiograms by injecting opaque medium through the cholecystostomy tube (Figures 7 and 8) showed normal configuration of the whole biliary tree. The cholecystostomy tube was then removed. The patient left the hospital without complaint.

Comments

The pancreas is a rare location for primary echinococcus cyst and comprises 0.07% of all cases

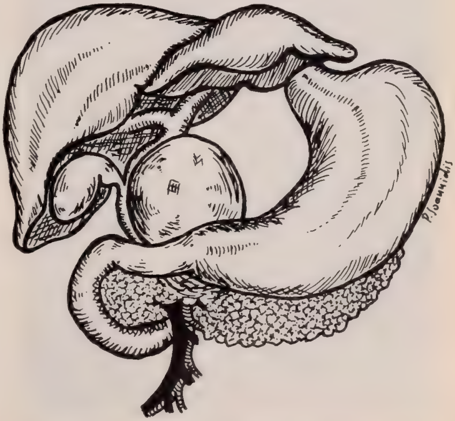


FIG. 3. Appearance of the pancreas after cutting adhesions.

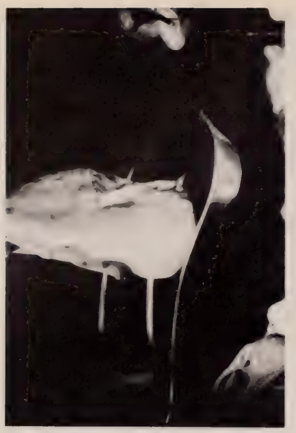


FIG. 4. Germinal layer after removal.

of primary hydatid disease. A primary location of hydatid disease in the pancreas presumably results from arterial transport of the embryo to the pancreatic tissue. When located in the pancreatic head, the cyst may compress the bile duct, occluding it and producing cholangitis. A complement fixation test (Weinberg) and the response to intradermal injection of cyst fluid (Casoni test) are positive in the vast majority of patients. Eosinophilia occurs in one-fourth to one-half the cases. Several serologic tests indicating hydatid infection are also available, for example the indirect hemaglutination test and the recently developed immunoelectrophoretic assay. Ultra sonography and computerized tomography may demonstrate with great accuracy the cystic mass as well as the thickness of cystic wall. The operative diagnosis is made by aspirating the clear waterlike fluid containing daughter cysts from the cystic mass. The diagnosis is further confirmed by histological examination of part of the cystic wall. The choice of the proper surgical treatment for hydatid disease of the pancreas depends upon the consistency of the underlying tissue, as well as the relationship of hydatid cyst to the pancreatic ducts.

Resection of the cyst—cystectomy—is practiced only in cases of superficial or pedunculated cysts. In the remaining cases, this method is to be condemned because of the danger of hemorrhage and injury to the pancreatic tissue and ducts. In the majority of cases, the first step should be evacuation of the cyst. Special care is necessary because of the risk of penetrating the pancreatic ducts which may be displaced by the cyst or included in

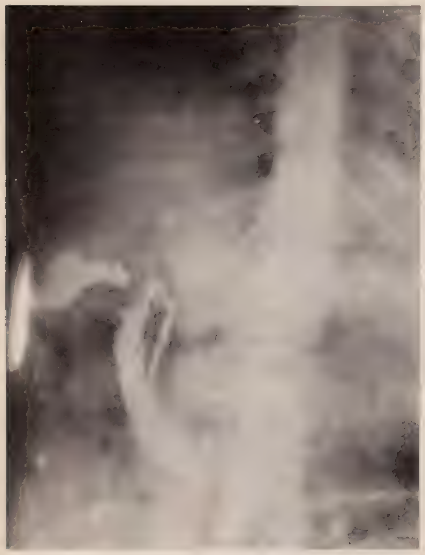


FIG. 5. The first cholangiogram.

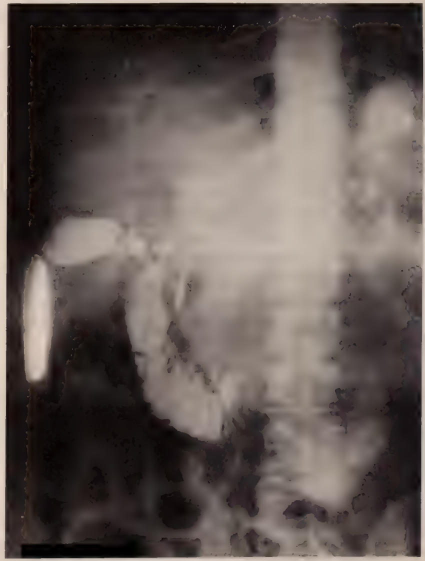
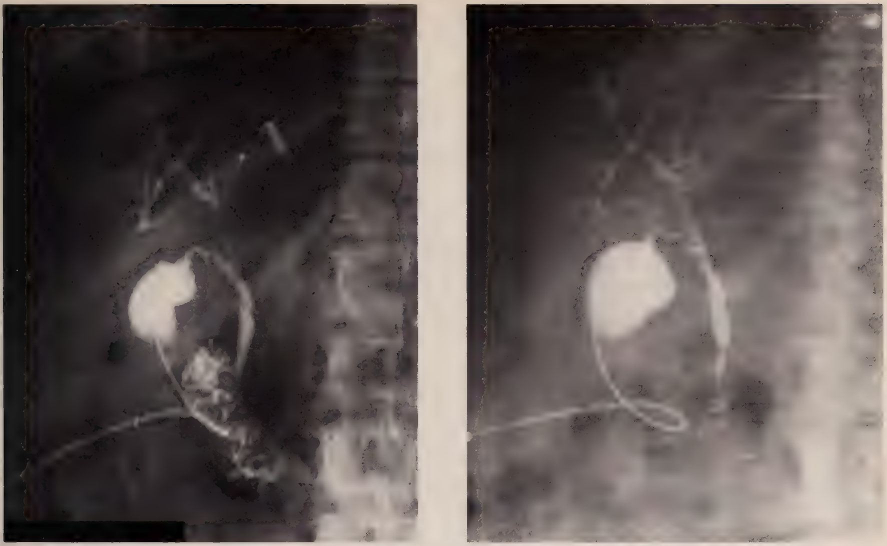


FIG. 6. The second cholangiogram.



FIGS. 7 and 8. Postoperative cholangiogram showing normal configuration of the whole biliary tree.

its adventitial layer. The immediate risk of evacuation is the contamination of the operative field with hydatid scolices. To guard against this, various scolicidal agents have been used. Many surgeons, however, regard these agents as contraindicated in cases of pancreatic cysts because injection into the cyst frequently causes pancreatitis. The treatment of the evacuated residual cavity depends on the state of the cysts and whether there is communication of the cyst with the pancreatic ducts. Information about this can be obtained by injecting opaque medium without pressure into the remaining cavity. One of the following methods can be employed for the treatment of the residual cavity:

1. Internal suture—capitonnage of the adventitial layer of the cyst is indicated in noninfected case. By eliminating the residual cavity, convalescence and hospitalization are shortened.

2. Partial cystectomy with primary suture. This method is indicated in superficial cyst. The superficial part of adventitia can be resected, and the remaining cavity can be obliterated by suture. Care should be taken not to include pancreatic tissue or ducts in the suture line.

3. Partial cystectomy with drainage. In a limited number of cases it may be advisable, after partial cystectomy, to insert a tube into the cavity and exteriorize it. This method may be employed in cases of partially superficial cysts.

4. Marsupialisation is indicated in large calcified or infected cysts which require wide external drainage. Marsupialization results in long hospitalization.

5. Omentoplasty was first practiced in late 1948 in cases of pancreatic hydatid disease. An adequate-sized piece of greater omentum with good blood supply is selected and spread into the residual cavity. A small drain is also inserted. This technique requires shorter hospital stays than marsupialization.

6. Cystojejunostomy can be used in selected cases where communication between the cyst and pancreatic ducts exists. The evacuated cyst is internally anastomosed to a jejunal loop.

In the case reported here, simple drainage and fixation of the cyst was employed with excellent results.

Summary

A patient was operated on because of epigastric pain, fever, and jaundice. At laparotomy a primary echinococcus cyst of the pancreatic head, compressing the common bile duct and resulting in cholangitis, was found. The case was success-

fully treated by removal of the mother cyst and drainage of the residual cavity.

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Submitted for publication May 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Tubulovillous Adenoma of the Papilla of Vater: A Case with Malignant Changes, Managed with Local Resection

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Introduction

In 1884 Toely described the first benign tumor of the papilla of Vater. These tumors, representing less than 3% of all tumors of the papilla of Vater (1), are very rare and consequently the literature on them is relatively limited (2, 3). Clinically they can give rise to gastrointestinal bleeding, thus occurring with hematemesis or melena, but as a rule, because of their location, they obstruct the distal common bile duct, resulting in progressive jaundice occasionally accompanied by biliary colic.

The case reported here is that of a patient with a tubulovillous adenoma of the papilla of Vater with painless progressive obstructive jaundice; the condition was managed with local resection and intraduodenal reimplantation of the common bile and pancreatic duct. Subsequent histology showed that the removed adenoma contained areas with malignant transformation.

Case Report

A 53-year-old woman was referred to the Surgical Gastroenterological Department, Aalborg Hospital, with the diagnosis of obstructive jaundice. There was no previous history until a month before referral, when progressive painless jaundice started, accompanied by clinical and biochemical obstructive features.

Laboratory data (normal range in brackets) included: Bilirubin 450 μmol/l (<21 μmol/l), alkaline phosphatase 747 μ/l (70–275 μ/l) amylase 95 μ/l (100–360 μ/l), ASAT 32 μ/l (10–40 μ/l), LDH 384 μ/l (<450 μ/l). Full blood count, urea-creatinine, and electrolytes were within normal limits.

Physical examination revealed no significant physical signs other than the deep jaundice.

Without further diagnostic investigation the patient was submitted to exploratory laparotomy through a right-sided subcostal incision. A grossly dilated gallbladder was aspirated containing 400 ml of bile. No stones could be demonstrated. A soft mass could be felt in the second part of the duodenum. A longitudinal duodenotomy exposed a pedunculated tumor which looked benign and which macroscopically and by palpation was very similar to villous adenomas seen in the colon and rectum (Fig. 1). The origin of the tumor in the papilla of Vater was confirmed by the passage of a probe in the distal choledochus through a separate choledochotomy, emerging eventually through the tumor in the duodenum. A frozen section from the top of the tumor showed no malignancy.

Local resection of the tumor through the duodenum was carried out; the distal choledochus and pancreatic ducts were sharply divided just proximal to their entrance in the duodenal wall (Fig. 2). Resection of healthy tissue was confirmed by frozen section. The ducts were reimplanted locally. Stents were used for both of them. The common bile duct, with a diameter of 20 mm, was intubated with the long peripheral limb of a No. 14 T-drain inserted through the choledochotomy.

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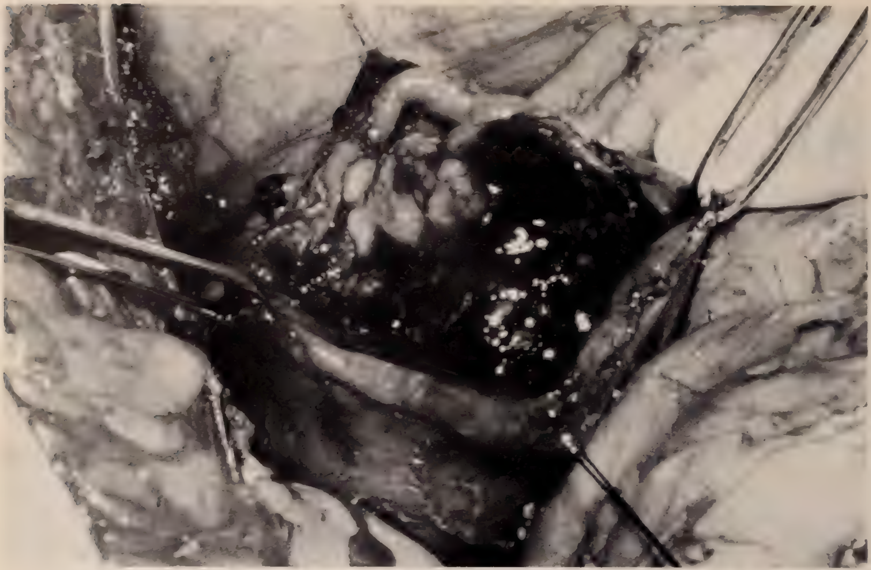

FIG. 1. A tubulovillous adenoma of the papilla of Vater as seen intraoperatively through a longitudinal duodenotomy.

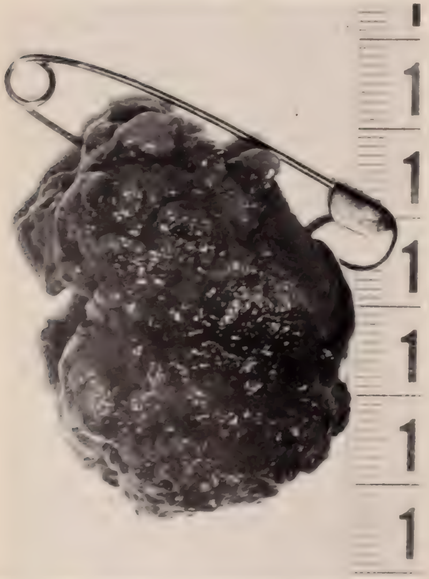

FIG. 2. Local resection of a tubulovillous adenoma of the papilla of Vater. Operative specimen.

The pancreatic duct, 6 mm in diameter, was stented by a No. 8 polyethylene baby feeding tube. Reimplantation was carried out with 4-0 Dexon interrupted sutures. The duodenum was closed in two layers. A suction drain was left in Morrison's pouch.

The patient's postoperative course was complicated by wound sepsis, necessitating drainage. The T-drain was removed on the eleventh day. The patient was discharged on the fifteenth postoperative day. Five weeks later she was without complaint. Laboratory data at that time included bilirubin 15 μmol/l, alkaline phosphatase 300 μ/l, ASAT 23 μ/l. She was given an appointment for four months from that date for endoscopy and removal of the pancreatic stent if found in situ.

Pathology

The specimen was a pedunculated, lobulated tumor measuring 4½ × 3½ × 2 cm. The tumor was composed of tubular and villous structures (Fig. 3), covered by a tall columnar epithelium, in some areas containing goblet cells, in other areas Paneth cells. This epithelium showed dysplasia varying from slight to severe, with nuclear stratification, hyperchromatism, increased mitotic activity, and secondary gland formation. The cen-

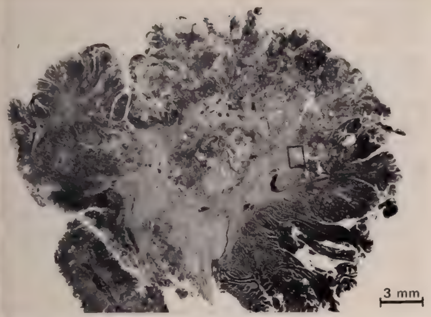

FIG. 3. Low-power view of the pedunculated tumor. The tumor consists of tubular and villous structures. Framed area demonstrates transition to adenocarcinoma invading the submucosa (hematoxylin and eosin ×5).

tral portion showed evidence of invasive adenocarcinoma (Fig. 4) penetrating the submucosa and the superficial muscularis propria.

Discussion

Adenomas arising from the papilla of Vater, the duodenum, and the small intestine in general, like the much more common adenomas of the colon, degenerate into adenocarcinoma (4, 5) at a high rate. Bearing this in mind, we consider our case to be identical (6) or similar (7) to earlier case reports, and one that moreover affords an opportunity for discussion of management of these uncommon lesions.

According to the largest recently published series on adenomas of the papilla of Vater (8), the tumors are asymptomatic until they grow large enough to produce symptomatology related to common bile duct compression-obstruction. At this stage, when the patient is jaundiced, duodenoscopy leads to accurate diagnosis and ERCP, if cannulation of the papilla is possible, can provide information regarding the possible extent of the tumor to the distal common bile and pancreatic duct.

Unfortunately none of the currently available diagnostic procedures was carried out on our patient, since we decided to explore promptly. We believe that an accurate preoperative diagnosis would not have altered the treatment.

The intraoperative diagnosis of an adenoma of the papilla of Vater is generally without difficulty. Symptomatic adenomas of the papilla are usually big enough not to be missed at careful exploration following a wide Kocher maneuver. The opposite has been reported in the past (3). Certainly small soft tumors can escape detection, especially if competent cause for the patient's jaundice is present and already found at exploration. If in doubt, a duodenotomy is absolutely indicated.

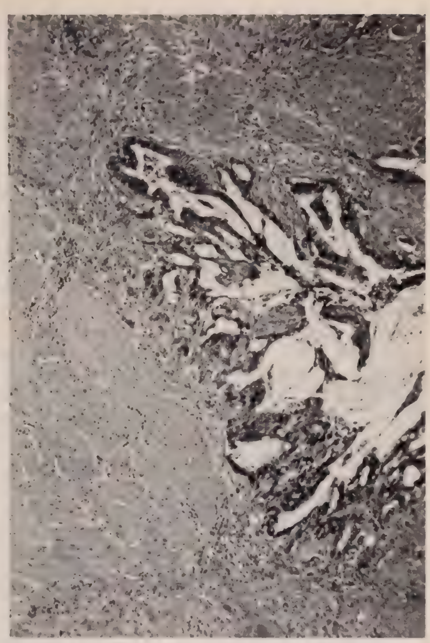

FIG. 4. Framed area of fig. 3 showing adenocarcinoma invading the submucosa (hematoxylin and eosin ×112).

Regarding surgical management, malignancy should always be suspected in adenomas. If macroscopically obvious, the case should be considered an ampullary carcinoma and should be treated accordingly, taking into account all the pros and cons of pancreaticoduodenectomy versus local resection. If in doubt, representative specimens from the tumor should be subjected to frozen section, but even then accurate diagnosis cannot always be guaranteed, as occurred in the case presented here.

Surgeons should be aware of the several pitfalls of the frozen-section diagnosis of the adenoma of papilla of Vater and should be prepared to alter management should the paraffin-section diagnosis show malignant foci not detected by the initial frozen section. If this is the case, the choice is between an early reoperation and radical pancreaticoduodenectomy and a conservative policy of close follow-up and management of subsequent local recurrence. Pathology can influence the decision by recreating the extent of invasion, but this is sometimes misleading in regard to the prognosis (9).

Local resection with transduodenal reimplantation of the involved duct, we believe, is the method of choice in all cases having a benign appearance. The tumor should be considered macroscopically benign if it is not fixed or does not invade the adjacent tissues and when no areas of ulceration-induration can be detected. The resection may be local but should be radical. Removal of the adenoma with healthy tissue both on the duodenal and on the ductal side should be confirmed by frozen section, as was done in this case.

Local resection has been proved adequate in cases with in situ carcinoma. In some series local resection had survival rates comparable to pancreaticoduodenectomy (10). A disadvantage of the procedure is the observed incidence of subsequent reoperations (10) but this must be weighed against the advantage of lower morbidity and mortality. The alleged tendency of the benign tumors of the papilla of Vater to recur (2, 11) is best explained either by the fact that they harbor malignant foci or by the fact that they are initially inadequately excised.

Reimplantation of both the common bile and the pancreatic duct has been done over stents. Stents are recommended as "supporting healing" but no documentation of their benefit can be found in the literature.

Careful follow-up of these cases by repeated endoscopic examination is mandatory for the early detection of local recurrence.

Summary

A case of a tubulovillous adenoma of the papilla of Vater with malignant changes invading the submucosa and the superficial muscularis propria is described. The patient presented clinically with painless, progressive, obstructive jaundice. Local resection followed by transduodenal reimplantation of the common bile and pancreatic duct to the duodenal wall was carried out, with good immediate postoperative results.

The case illustrates the frequency of invasive cancer in adenomas in the small bowel. The place of local resection in the surgical management of these uncommon tumors is discussed, focussing especially on such tumors located at the duodenum and arising from the papilla of Vater.

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Submitted for publication May 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Distribution of G-Cells in the Gastrointestinal Mucosa of the Uremic Patient

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Gastrointestinal symptoms in uremic patients are frequent but little is known concerning their pathogenesis.

This is a report of the morphology of the gastric mucosa in uremic patients, with special attention to the distribution of G and D cells within it (1–3).

Material and Methods

Six patients, three male and three female, in renal failure due to chronic glomerulonephritis were studied. The patients' ages ranged from 25 to 45; the average age was 40. All were receiving four hours of renal dialysis with Gambro AK 10 single-unit machines three times a week. The dialysis solution had the following composition:

Na^+	138 mEq/L
K^+	2 mEq/L
Ca^{2+}	4 mEq/L
Mg^{2+}	1.5 mEq/L
Cl^-	107.5 mEq/L
Dextrose	12 gr/L

All patients consistently maintained normal blood pressures (mean, 120 mm Hg) without antihypertensive medication. None of the patients were receiving antacids. Blood chemistries in general were in normal ranges; the average values were red-cell count, 3.0 million/mL; blood glucose, 75 mg%; blood urea nitrogen, 15 mg%; serum creatinine, 1.1 gm%; sodium, 130 mEq/L; potassium, 4 mEq/L; serum glutamic oxaloacetic transaminase, 4 μ/mL; serum glutamic pyruvic transaminase, 3 μ/mL.

Endoscopic examinations were performed with an Olympus GIF-Q gastroscope. Biopsies were obtained with a punch forceps at five selected areas: (a) duodenal bulb; (b) pylorus; (c) gastric antrum on the lesser curvature; (d) gastric body on the lesser curvature; (e) gastric body on the greater curvature. Biopsies were oriented with the mucosal side upward and fixed in Bouin solution for 25 hrs. The specimens were rinsed, dehydrated in alcohol and xylene solutions, and embedded in paraffin. Serial sections, 5 μ thick, were cut using a Bright microtome. Conventional histology (hematoxylin and eosin) and immunochemistry (peroxidase, antiperoxidase PAP) were performed. The sections were hydrated and then incubated for 12 hours with the primary antibody (for gastrin). All antibodies used were highly diluted and showed high specificity (4).

The sections were rinsed in phosphate buffer (PBS) and incubated with a second antirabbit antibody serum (for somatostatin) at room temperature. The tissue was then incubated with PAP complex for 30 minutes at room temperature and, finally, incubated with diaminobenzidine solution (DAB 50 ng in 100 mL). The sections were

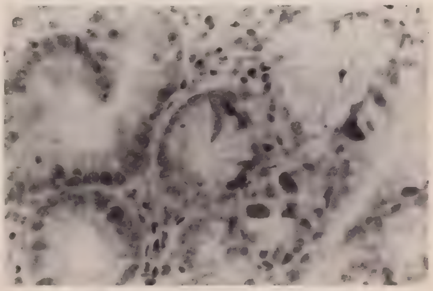

FIG. 1. Antral mucosa showing G-cells.

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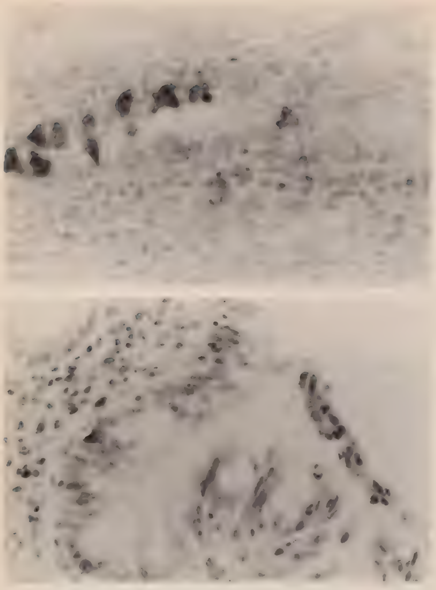

FIGS. 2–3. Mucosa of corpus showing numerous G-cells scattered in areas of metaplasia.

mounted in a permanent medium (Canada balsam) and observed under Leitz microscope (Orthoplan) for identification of G and D cells.

Results

In all patients examined, chronic inflammation of the gastric and duodenal mucosa, generally confined to the superficial zone of the lamina propria, could be detected. There were various degrees of dysplasia of the foveolar epithelium as well as pseudopyloric metaplasia in the gastric antrum. In two patients there were signs of active gastritis scattered throughout the mucosa, i.e. edema, granulocytic infiltrations, inflammatory cells in the epithelium, as well as basal congestion. In two other patients there were foci of intestinal metaplasia.

Immunohistochemical studies of the antral sections demonstrated populations of hyperplastic G-cells (Figure 1).

Immunohistochemical studies of sections from the body of the stomach revealed numerous G-cells scattered in areas of metaplasia (Figures 2 and 3). These were more numerous in areas of pseudopyloric than intestinal metaplasia. The density of G-cells in the duodenum appeared normal (Figure 4). On the other hand, D cells were extremely rare in the antrum as well as in areas of metaplasia. This distribution of G- and D-cells observed in the uremic patient presents an abnormal pattern and correlates with increases in serum gastrin levels which have been reported in uremia.

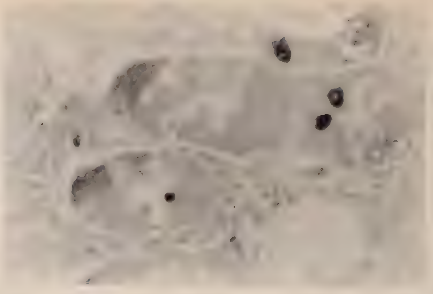

FIG. 4. Duodenal mucosa showing normal density of G-cells.

Summary and Conclusions

Antral G cell hyperplasia in the gastric antrum as well as in areas of metaplasia in the body of the stomach were observed in six uremic patients receiving chronic dialysis. On the other hand, D cells were encountered with extreme rarity. This abnormal pattern of gastrointestinal endocrine cells may explain the hypergastrinemia as well as poorly defined gastrointestinal complaints observed clinically in these patients.

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Submitted for publication June 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Ophthalmologic Notes

Keith M. Zinn, M.D., Editor

Postgonococcal Ophthalmia

Harold S. Raucher, M.D.

Pregnant women frequently have infections of the cervix caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or both. Their infants are at risk of acquiring neonatal eye infections during passage through the birth canal.

A well-known syndrome in adult males, postgonococcal urethritis, results from coinfection with two pathogens. Following eradication of gonococcal urethritis, a milder urethritis often caused by *C. trachomatis* becomes apparent. In a similar fashion, neonates born to mothers with concurrent gonococcal and chlamydial cervical infection could develop biphasic conjunctival illness. To our knowledge, however, this has not been reported. The case of an infant found to have inclusion conjunctivitis after successful treatment of *Neisseria* ophthalmia is presented.

Case Report

A 2920-gram boy was born vaginally at term to a 17-year-old woman at another hospital. He received silver nitrate eye prophylaxis. On the second day of life he was noted to have a yellow purulent discharge from the left eye, but was not treated and was discharged with the mother the next day. On the fourth day, the infant was brought to The Mount Sinai Hospital, New York, for worsening of the eye discharge and swelling of the lids.

The mother recalled a yellow vaginal discharge during the third month of pregnancy, but, to her knowledge, had not been exposed to venereal disease.

The child had briefly lived at home with his mother, grandmother, and a cousin. No one was ill. The infant had not been febrile and had fed well.

On examination, the child was alert and active. The rectal temperature was 36.8°C and the weight was 2940 grams. The eyelids on the left were edematous and shut, sealed by a thick, yellow exudate. When the eyes were opened, copious amounts of pus were exuded. The conjunctiva was markedly injected, with chemosis. The left pupil and cornea appeared normal, as did the right eye. The remainder of the examination revealed no abnormality.

The peripheral white-cell count was 14,000/mm^3 with 44% segmented neutrophils, 1% bands, 43% lymphocytes, 9% monocytes, and 3% eosinophils. Gram stain of the eye discharge showed numerous polymorphonuclear leukocytes and large numbers of gram-negative diplococci morphologically typical of *Neisseria* species and presumed to be gonococci. Many organisms were intracellular.

Therapy with intravenous aqueous penicillin G, 35,000 units every six hours (50,000 units/kg/day), was begun. The eyes were treated locally with penicillin eyedrops and saline irrigations. Cultures of the child's conjunctiva and blood and the mother's cervix and rectum at the time of admission failed to grow *N. gonorrhoeae*. However, *N. meningitidis* was present in the mother's pharynx.

Within twenty-four hours, there was dramatic improvement of the left eye. By the fourth hospital day the eyelids were no longer edematous, the discharge had ceased, and the conjunctiva was only minimally inflamed. However, on the following day (eighth day of life), the right eye was found to have a mucopurulent discharge and conjunctival infection. Two days later a small amount of discharge from the left eye also appeared. Gram stains of the discharge from each eye revealed neutrophils and mononuclear cells,

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but no diplococci. Epithelial cells with intracytoplasmic inclusions and nuclear capping characteristic of chlamydial infection were seen on Giemsa stain. Culture for bacteria was negative. Isolation of *C. trachomatis* was not attempted.

The parenteral and topical penicillin were stopped and sulfacetamide eyedrops were begun. Both eyes improved, showing a marked decrease in discharge over the next three days. Although a scant discharge remained bilaterally, the infant was sent home on the tenth hospital day. He was free of eye disease when seen as an outpatient at the completion of three weeks of topical therapy.

Discussion

Conjunctivitis in the newborn is frequently caused by *N. gonorrhoeae* or *C. trachomatis*. Yet few examples of concurrent infection with these pathogens have been described. Armstrong et al. (1) identified three neonates with ophthalmia having either smear or culture indicative of gonococci and inclusions on conjunctival scraping. The clinical features of only one case were described. Another three infants with conjunctivitis and conjunctival culture simultaneously yielding *N. gonorrhoeae* and *C. trachomatis* were reported by Rees et al. (2). As with Armstrong's patient, however, the eye discharge in each case began after six to seven days and was not biphasic. The sequential appearance of gonococcal and chlamydial conjunctivitis in the same neonate has not, to our knowledge, been reported.

Asymptomatic cervical infections due to *Chlamydia* and *N. gonorrhoeae* are common in pregnant women. A large national screening program a decade ago revealed that 2.3% to 3.9% of women seen at a variety of prenatal clinics and private obstetrical offices were infected with *N. gonorrhoeae* (3). Now, reflecting the steadily increasing incidence of gonorrhea in this country, an even larger number of pregnant women may have inapparent infection. Similarly, *C. trachomatis* was cultured from the cervices of 2% to 12.7% of healthy pregnant women (4–7). That both agents often are found in the same woman indicates a common venereal route of infection. In sexually-transmitted-disease clinics, from 33% to 63% of women harboring *N. gonorrhoeae* are also culture-positive for chlamydia (8, 9). The incidence of double infection is likely lower in a prenatal clinic setting. In one study (5), both organisms were cultured from the cervix in 0.6% of gravid women.

The conjunctivae of an infant born vaginally to such a mother might become colonized with both pathogens. The short incubation period of the gonococcus (2–3 days) explains its early presentation as ophthalmia. When treated appropriately, there is prompt clinical improvement of eye findings. Meanwhile, *Chlamydia* persist on the conjunctiva, since they are not killed by penicillin. Because of the incubation period (5–12 days), the chlamydial conjunctivitis is first noted only after the resolution of the gonococcal ophthalmia.

Concurrent infection with both a short-incubating, penicillin-sensitive agent and a long-incubating, penicillin-resistant one has been well documented in the pathogenesis of postgonococcal urethritis (10). As a result of widespread usage of silver nitrate and other prophylactic agents, however, the incidence of gonococcal ophthalmia is currently low. *Chlamydia* infection is not prevented by silver nitrate or intramuscular penicillin. This may explain why postgonococcal ophthalmia is uncommon, while chlamydial conjunctivitis alone is frequently seen.

We realize that the validity of our report would have been strengthened if the gonococcus had been grown from the infant's eye. *N. meningitidis* (11) and *N. catarrhalis* (12) have rarely caused neonatal ophthalmia and cannot be distinguished from *N. gonorrhoeae* on gram stain alone. Also, although seeing inclusions on Giemsa stain is considered diagnostic of chlamydial eye infection, here too a positive culture supplies further proof of infection.

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Submitted for publication May 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Topical Conjunctival Corticosteroid Therapy for Malignant Atrophic Papulosis (Kohlmeier-Degos Disease)

JUAN ORELLANA, M.D., AND ALAN H. FRIEDMAN, M.D.

Abstract

A female patient with a ten-year history of Kohlmeier-Degos disease (malignant atrophic papulosis) presented with episcleral-conjunctival plaques. Six weeks of therapy with topical steroids and lubricants alleviated this patient's symptoms and successfully ameliorated the ocular lesions.

In 1941, Kohlmeier described a patient with a papular skin rash and intestinal perforations (1). One year later, Degos et al. (2) described a similar patient and named the condition atrophic papulosquamous dermatitis. Patients with this rare disease exhibit endovasculitis affecting the skin, central nervous system (3–7), heart (4), bladder (8), intestines, and eyes (9, 10). It is frequently a fatal disorder, afflicting young and middle-aged males three times more often than females.

A patient who had typical ocular findings and was successfully treated with topical steroids and lubricants is described here.

Case Report

H.R., a 57-year-old Hispanic female, was diagnosed as having malignant atrophic papulosis (Kohlmeier-Degos' disease) ten years ago based on pathologic examination of skin lesions located on the palmar aspects of her hands.

For the past eleven years, she has periodically suffered from skin lesions which were most prominent on her trunk, face, and extremities, including the palms and soles. During this time, she never experienced acute gastrointestinal disease. A large-bowel biopsy was performed in 1978 at The Mount Sinai Hospital.

In September 1979 she came to The Mount Sinai Hospital eye clinic with the chief complaint of having had a gritty, foreign-body sensation in her right eye for three weeks. In addition, she had noted redness in this eye for three weeks. She had never previously experienced a red eye or an ocular foreign-body sensation.

Except for her history of Kohlmeier-Degos' disease, she had a negative medical history. Her family medical and ocular history was negative.

An ophthalmologic examination revealed corrected visual acuity of 20/25 in each eye. Near vision was Jaeger 1 in each eye with correction. Ductions and versions were intact and she was orthophoric for both near and distance. Her pupils reacted equally to light and accommodation. External examination revealed slightly elevated papular lesions at the lateral canthi of both eyes. Several flat circular lesions with a central white area were present over the left upper lid.

Slit-lamp biomicroscopy revealed that the left eye possessed a normal anterior segment. The right eye demonstrated several avascular papular-nodular lesions 0.5 mm × 0.5 mm in size. They appeared to involve the episclera and conjunctiva. They were firm, nonmovable, and not tender. These lesions were surrounded by injected conjunctiva (Fig. 1). Investigation of the tear film demonstrated a tear break-up time of 6 seconds in the right eye and 15 seconds in the left eye. A Schirmer test (performed without topical anesthesia) showed 25 mm of wetting in the right eye and 15 mm in the left eye after five minutes. A decreased but present tear meniscus was present bilaterally. Funduscopic examination revealed normal discs, maculae, and vasculature without any evidence of chorioretinal scars or avascular

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Supported by an unrestricted grant from Fight for Sight, Inc.

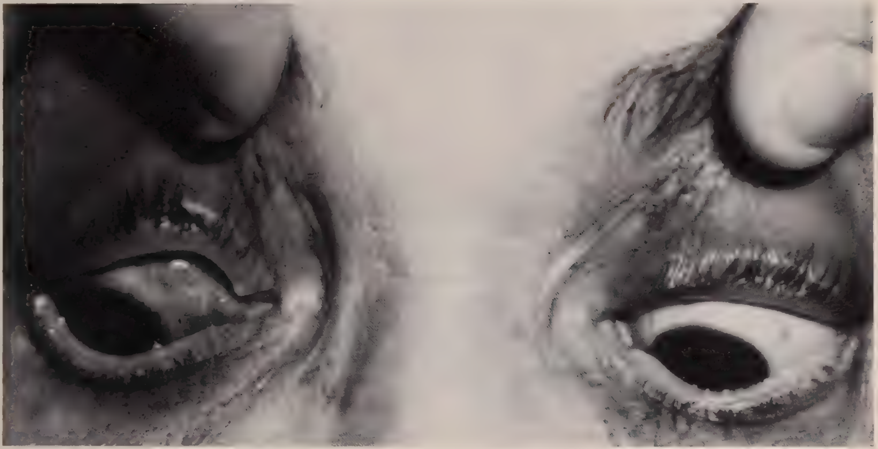

FIG. 1. The right eye demonstrates redness and several episcleral-conjunctival plaques.

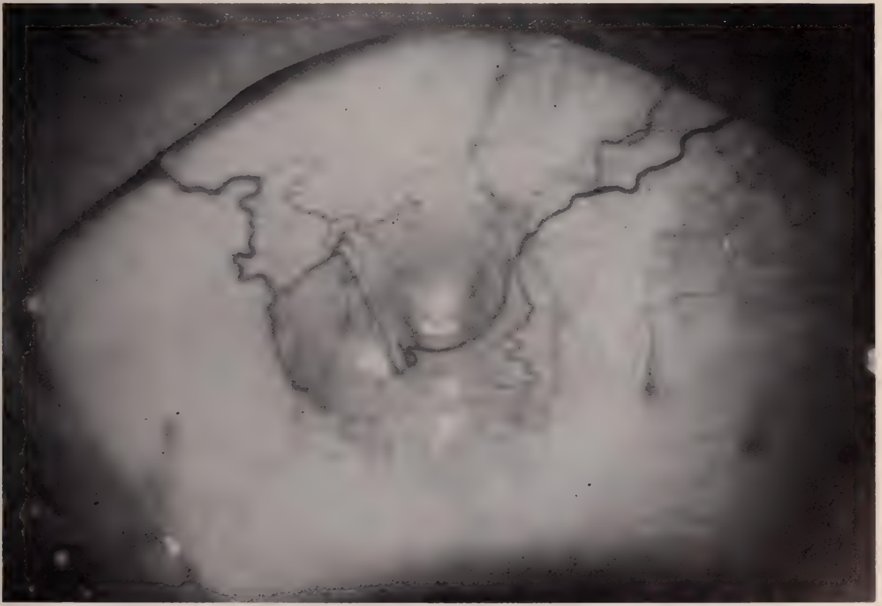

FIG. 2. After two weeks of topical dexamethasone therapy, regression of the lesions seen in Figure 1 has started.

areas in either eye. All laboratory investigations were normal. The patient refused a diagnostic conjunctival biopsy.

The patient was started on one drop of topical dexamethasone phosphate solution 0.1% every two hours in the right eye. After two weeks of this treatment, the lesions appeared smaller and the conjunctival reaction was diminished (Fig. 2). A topical liquid lubricant, Tearisol, was added to decrease the foreign-body sensation, and the application of steroids was reduced to every four hours. During subsequent weeks, treatment with steroids was gradually tapered off; the lubricants, however, were continued. One year after her ocular lesions resolved, she had not suffered any recurrence and was still using the lubricants. Her right eye demonstrated several telangiectatic vessels over the site of the papular lesions. The lesions were nearly flat and pinkish-white in color (Fig. 3). In May 1981, in Puerto Rico, she suffered an acute episode of intestinal perforation from which she died. An autopsy was not performed.

Discussion

Histopathologic studies in the Kohlmeier-Degos syndrome reveal involvement of arterioles and medium-sized arteries with a deposition of fibrous tissue between the endothelium and the internal elastic lamina (5). This deposition gradually decreases the vessel lumen, which in turn may lead to infarction of the tissues downstream. This vascular change is most commonly seen in the skin and the gastrointestinal systems. It is a disease of young adults, although it has been reported in patients over 55 years of age. In the 70 cases reported so far, men outnumber women.

The disease can be fatal, especially when intestinal perforation (4, 11, 12) or cerebral infarction occurs (6, 7). As contrasted to polyarteritis nodosa, there is no acute inflammation of the vessel wall. The vessel wall may possess lymphocytes, histiocytes, or some neutrophils; however, no perivascular inflammation is visible (5). The small and medium-sized blood vessels demon-

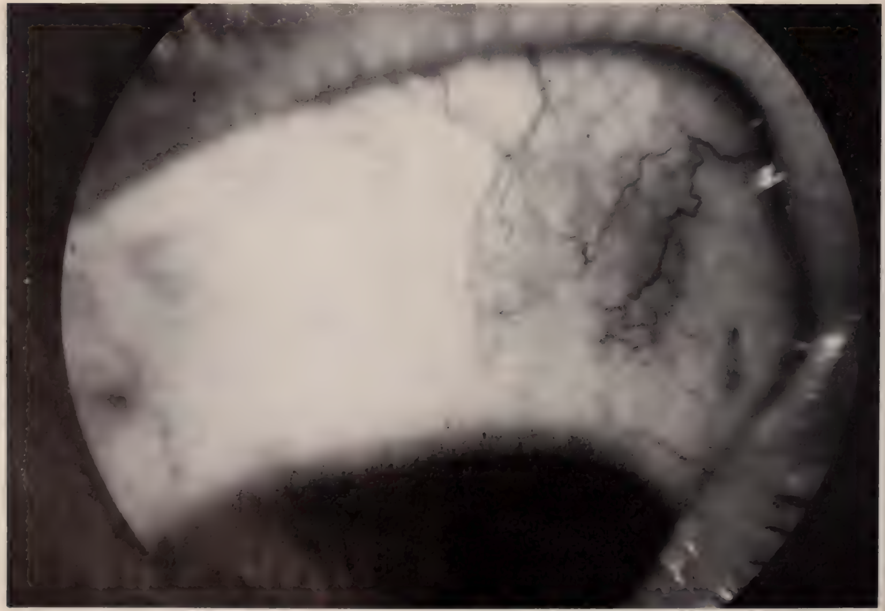

FIG. 3. At the end of the sixth week of treatment of the episcleral-conjunctival lesions with topical steroids and topical lubricants, residual conjunctival telangiectasia is seen over the site of the original lesions.

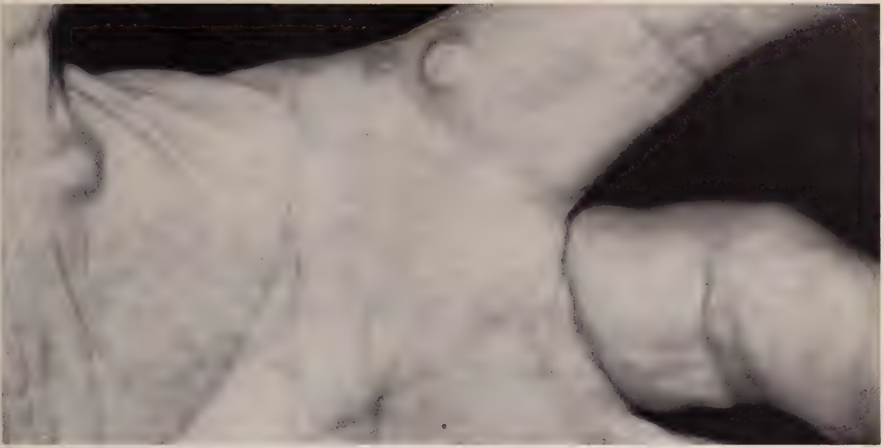

FIG. 4. Umbilicated papular lesions are visible on the skin of the patient's thumb and index fingers.

strate endothelial-cell swelling, intimal proliferation, and thrombosis (3). Infrequently, necrotizing vasculitis has been reported (13, 44) in addition to mucin deposition in the perivascular space (15). These vascular changes have been seen in many organs: skin, central nervous system, kidney (4), bladder (8), gastrointestinal tract, gallbladder (16), mesentery (16), spleen, pancreas (17). No etiology has been discovered for this disease.

Initial presentation involves the skin (8, 13, 18, 19), which usually displays less than a hundred lesions. The lesions are slightly elevated papules, several millimeters in size and distributed in groups. The papules may remain from several days to several months and then undergo central umbilication resolving to a slightly elevated lesion with a violaceous margin surrounding a white center (11, 12, 15).

Biopsy of the palmar skin lesions in this patient guided the diagnosis of malignant atrophic palpulosis, epidermal atrophy, and dermal sclerosis with acellular fibrous thrombus occluding small arteries in the lower third of the reticular dermis. The rectal biopsy demonstrated small vessel fibrosis in the adventitia and round-cell infiltration in the substantia propia. No evidence of active inflammation or ischemia was seen. When stained for mucin with alcian blue, some sections demonstrated mucin deposits in the perivascular space. This suggests the diagnosis of malignant atrophic papulosis when coupled with the clinical appearance of the skin, conjunctival lesions, and skin pathology.

The ocular signs of Kohlmeier-Degos' disease include bulbar conjunctival capillary microaneurysms (3, 5, 10, 11, 15), 20 to 24 episcleral plaques surrounded by telangiectasia (3, 24–27), pigmentary choroiditis (10, 11), avascular gray areas in the fundus (5), papilledema (3), and third nerve palsy. Optic atrophy can be seen in the terminal stages of the disease (28). Henkind and Clark (10) noted subendothelial fibrosis in the anterior episcleral vessels, large retinal vessels, and choroidal arterioles similar to that seen in the brain vasculature. This patient demonstrated lid lesions on both upper eyelids. These, as well as the other lesions, had appeared and regressed over the years without any treatment. In addition, this patient demonstrated episcleral plaques which responded to intense topical steroid therapy. No evidence of choroiditis or avascular patches was present in this patient. It is notable that the patient did not experience an episode of intestinal perforation until the fatal episode many years after the onset of her disease. Only one other patient did not have episodes of intestinal perforation while under care for his disease (29).

The response to steroids observed in this case is contrary to that reported by other workers who have tried parenteral steroid therapy (12, 18, 24). Topical steroids have not previously been given to patients with episcleral plaques. The topical therapy may have delayed further endothelial fibrosis and thus prevented subsequent tissue infarction in the conjunctiva (3, 24). If her lesions were caused by a necrotizing vasculitis or mucin deposition, as has been seen in some cases of Kohlmeier-Degos' disease, topical corticosteroid therapy would be of great assistance. The topical lubricants merely assisted in alleviating the foreign-body sensation due to a disrupted tear film. The telangiectatic vessels which remained may be the sequelae of the resolution of episcleral plaques and thus account for the prior observations of bulbar telangiectasia.

Acknowledgments

The authors would like to thank Steven M. Podos, M.D., Michael Newton, M.D., Mr. Robert Campanile, Mr. Howard Radzyner, and Ms. Elizabeth Wilkins for their help.

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Submitted for publication February 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 1, January–February, 1983
Printed in U.S.A.

Malignant Hyperthermia: A Review of the Literature

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Abstract

Malignant hyperthermia is a rare pharmacogenetic disorder characterized by hyperpyrexia, muscle rigidity, tachycardia, and respiratory and metabolic acidosis. It occurs in response to a variety of inhalational anesthetics and muscle relaxants. Malignant hyperthermia represents an inborn error of skeletal muscle metabolism which renders the muscle susceptible to disturbances of intracellular calcium distribution. It is a catastrophic complication of surgery and carries a 28% mortality rate. Once suspected intraoperatively, all surgery and anesthesia are to be discontinued; the patient must be placed on 100% oxygen, cooled, given sodium bicarbonate and dantrolene, and carefully monitored. Preoperative detection is difficult, but a family history of malignant hyperthermia, abnormalities of back muscles, and elevated CPK are clues. The most accurate diagnostic test is skeletal muscle biopsy. For patients with known malignant hyperthermia, an operation should be performed only if absolutely necessary, and the patient premedicated with dantrolene.

Review of the Literature

Malignant hyperthermia, also known as acute familial peranesthetic rhabdomyolysis, is a rare pharmacogenetic syndrome characterized by a fulminant hypermetabolic crisis. Rapid rises in temperature of 102°F to 108°F occur in response to inhalational anesthetics such as methoxyflurane, enflurane, or ethyl ether or in response to muscle relaxants such as succinylcholine. Malignant hyperthermia is a catastrophic complication of induced anesthesia and surgery; it demands immediate management not only by the anesthesiologist but also by the surgeon.

Malignant hyperthermia was first described by Denborough, who reported the case of a 21-year-old male who developed fever, cyanosis, and tachycardia during anesthesia with halothane (1). The young man survived the episode, but his family history revealed ten relatives who had died after similar operative complications. The condition was transmitted through three generations and was inherited in an autosomal dominant fashion. Denborough's description of malignant hyperthermia led to worldwide awareness of the risks of genetic susceptibility to certain anesthetic agents and stressors. Since 1975 well over six hundred cases of malignant hyperthermia have been reported. The condition has an incidence of 1:15,000 in anesthetized children and 1:50,000 in anesthetized adults (2). The youngest patient described in the literature is an infant and the oldest a septuagenarian. The genetic inheritance is autosomal dominant but with reduced penetrance and variable expressivity (3). Although hereditary susceptibility can be traced in many cases, Schiller and Main (4) have recently demonstrated a viruslike crystalline structure in muscle biopsies taken from patients in the acute phase of malignant hyperthermia; Tseuda (5) has reported cases of malignant hyperthermia in two patients with Burkitt's lymphoma, which has an etiological association with Epstein-Barr virus, suggesting that malignant hyperthermia may be virally induced.

The exact pathogenesis of malignant hyperthermia is unknown. Kalow (6) has proposed that malignant hyperthermia is due to an inborn error of skeletal muscle metabolism which renders the muscle susceptible to disturbances of intracellular calcium distribution. In normal muscle contraction, calcium is released from the sarcoplasmic reticulum into the intracellular space. The ion activates myosin ATPase which converts ATP to ADP, phosphate, and heat. The calcium ions

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This paper was written when the author was a third-year student at the Mount Sinai School of Medicine.

are returned to the sarcoplasmic reticulum by means of an energy-dependent transport system, permitting muscle relaxation. Many researchers hypothesize that in malignant hyperthermia there is an unrestricted outflow of calcium from the sarcoplasmic reticulum as well as a failure of calcium reuptake by that membrane. Secondary to the activation of myosin ATPase and the conversion of ATP to ADP, vast quantities of heat are produced as well as muscular contraction and rigidity. Consequent to the significantly increased intracellular concentration of calcium is mitocondrial uptake of that ion and the disruption of oxidative phosphorylation. Anaerobic metabolism and metabolic acidosis ensue.

The Animal Model. The availability of an animal model has greatly enhanced the understanding of the pathophysiology of malignant hyperthermia. Hall (7) has induced malignant hyperthermia in certain breeds of pigs anesthetized with halothane or succinylcholine. He has shown that the underlying defect in malignant hyperthermia is the excessive concentration of mycoplasmic calcium. The porcine model has been instrumental in identifying triggering agents (Table 1) as well as leading to therapeutic trials with dantrolene sodium. The model has not, however, successfully defined the exact mechanism by which the calcium level is raised, nor the site and nature of the muscle abnormality. Further studies should expand our knowledge of the mechanisms involved.

While it cannot be unequivocally stated that the intracellular or membrane defects responsible for malignant hyperthermia are identical in pigs and humans, the extracellular manifestations are remarkably similar (3). Susceptible pigs and human beings respond to anesthetic agents with striking changes in metabolism, as manifested by increased production of heat. The hallmark of malignant hyperthermia is the fever generated. The higher the temperature, the greater the danger of mortality (3).

Diagnosis of the Condition. Malignant hyperthermia should be suspected intraoperatively or postoperatively by any unexplained rise in temperature. A temperature rise of .5°C over two successive 15-minute intervals is a warning requiring immediate evaluation. The anesthesiologist may notice the excessive heat of the sodium lime cannister on the anesthesia machine, while the surgeon notes increased warmth from the wound site, a hyperthermic liver, or hot, flushed skin. The higher temperatures tend to be induced by inhalational anesthetics as opposed to muscle relaxants, yet the latter are associated with an earlier onset of fever. The combined use of an inhalational anesthetic and muscle relaxant induced both the earliest onset of fever and the highest temperature (3).

TABLE I

Agents Implicated in Malignant Hyperthermia

Caffeine	Lidocaine (local)
Carbocaine (local)	Methoxyflurane
Curare	N-alkyl Nortoxiferine
Cyclopropane	Nitrous Oxide
D-Tudocurarine	Potassium Chloride
Diethyl ether	Spinal Analgesia
Enflurane	Stress
Ethylene	Succinylcholine
Gallamine	Thiopentone
Halothane	Trichloroethylene

From Schvaneveldt, J. A., et al. Malignant hyperpyrexia: an update for the otolaryngologist. Otolaryngology 1980; 88:921.

Tachycardia is the most consistent early evidence of malignant hyperthermia (8). Tachyarrhythmias, particularly of ventricular origin, may follow. Unless there is some obvious explanation for the arrythmia, malignant hyperthermia must always be suspected. Many fatal cases of malignant hyperthermia have occurred when triggering agents have been used for long periods despite the onset of tachycardia or other arrhythmia shortly after the administration of anesthesia begins (3). The tachycardia is not only due to a hyperthermic rigidity of heart muscle but is also secondary to fever and electrolyte abnormalities.

Complications. Muscle rigidity may be marked, or, like fever, may occasionally be absent. In susceptible patients succinylcholine is the agent most likely to induce a sudden boardlike rigidity. When nonpolarizing muscle relaxants are given in the hope of alleviating the stiffness, the rigidity worsens. Furthermore, if the patient suffers from polymyositis, or conditions that elevate calcium such as Paget's disease or hyperparathyroidism, there is a greater likelihood of developing intense muscle rigidity (8).

The susceptible patient may develop mottled cyanosis. This is due to peripheral vasoconstriction and accelerated oxygen consumption by rapidly metabolizing muscle cells. Arterial oxygen tensions may be reduced, although the PaO_2 may be normal even in the presence of cyanosis (3).

Excess carbon dioxide is produced by the hypermetabolizing muscle cells. $PaCO_2$ of up to 100 mm Hg can occur within a few minutes of induction and prior to the detection of elevated temperature. The body attempts to excrete the excess carbon dioxide with rapid, deep respirations, which result in respiratory acidosis. A profound fall in pH occurs not only because of the respiratory acidosis but also because of the metabolic acidosis, a consequence of accelerated lactic acid production by muscle cells. As Britt (3) reports, there is a statistically significant relationship between the fall in pH and mortality.

In malignant hyperthermia a wide range of electrolyte abnormalities occur (3). Secondary to the loss of sarcoplasmic integrity and increased mobilization of ions in the muscle cell, elevated serum levels of potassium, sodium, magnesium, calcium, CPK, and myoglobin are found. Increased serum concentrations of potassium and calcium are in part responsible for cardiac arythmias; myoglobin, having penetrated into the renal parenchyma, is responsible for constriction of the afferent arteriole. Such constriction produces progressively rising blood urea nitrogen and subsequent oliguria and anuria.

Finally, other conceivable complications of malignant hyperthermia include acute pulmonary edema, grand mal seizures, and impaired coagulation. Factor 8, fibrinogen, and platelet levels are greatly reduced; the cause remains unknown. Several researchers (9) have suggested that the impaired second wave platelet aggregation in patients susceptible to malignant hyperthermia may be an excellent screening test for malignant hyperthermia. This, however, has recently been proved erroneous (10).

The extent of malignant hyperthermia is proportional to the susceptibility of the subject and to the total dose of the anesthetic used (dose being defined as concentration times duration of administration). When malignant hyperthermia is fulminant—temperature increasing by 1°C per fifteen minutes, arterial pCO_2 greater than sixty torrs, base excess less than −5meq/L and falling—immediate intervention is required.

Therapy Plan. The following therapy plan has been developed (11):

1. Immediately discontinue anesthetic drugs and muscle relaxants and stop the operation.

2. Hyperventilate the patient with 100% oxygen using a vapor free anesthetic machine and a nonrebreathing circuit in order to correct the respiratory acidosis and arterial desaturation.

3. Secure the following lines: an electrocardiogram, temperature monitor, Foley catheter, and an arterial and central venous line.

4. Administer intravenous sodium bicarbonate. For a 70-kg adult it is reasonable to administer three ampules of sodium bicarbonate; for a child, 2 mEq/kg is the proper dose. These initial doses should then be titrated according to arterial pH and pCO_2. The bicarbonate not only corrects the underlying acidosis but also is effective in lowering serum potassium levels and preventing ventricular fibrillation.

5. Actively cool the patient with hypothermic blankets, place ice bags in the axilla and groin, and administer intravenously iced normal saline. The latter cools arterial blood, increases plasma volume, and helps insure an increased urinary output.

6. Initiate drug therapy with:

   (a) Dantrolene sodium, a lipid soluble hydantoin derivative. Dantrolene attenuates calcium release without affecting uptake by acting upon the connections between the transverse tubules and the terminal cisternae of the sarcoplasmic reticulum. Initially synthesized as a possible new antibiotic, dantrolene received FDA approval in January 1980 and is at present the treatment of choice for malignant hyperthermia. The initial intravenous dose is 1 mg/kg; if physiological abnormalities persist thereafter, the dose may be repeated up to a cumulative dose of 10 mg/kg.

   (b) Haloperidol, 2.5 mg intravenously. Haloperidol increases calcium reuptake by the sarcoplasmic reticulum and, by acting as a peripheral vasodilator, promotes heat loss.

   (c) Pronestyl, 0.5−1 mg/kg/min. Pronestyl also increases calcium reuptake by the sarcoplasmic reticulum. In addition, it is efficacious in treating arrhythmias.

   (d) Lasix 1 mg/kg, mannitol, and adequate hydration to promote diuresis and prevent myoglobin casts from forming in the kidney and producing renal failure.

In treating malignant hyperthermia one must be aware that overhydration can cause pulmonary edema, that vigorous cooling can lead to inadvertent hypothermia, and that potassium administration may be fatal. To prevent pulmonary edema, the central venous pressure must be monitored; to prevent inadvertent hypothermia, all cooling must cease when the patient's temperature reaches 101°F. And to prevent death from potassium administration, the treating physicians must realize that plasma potassium levels of 2 mEq/L are not uncommon in malignant hyperthermia and must not be treated—the reason being that potassium administration causes sudden fluxes in serum potassium levels and consequent ventricular fibrillation (3).

Detection of Susceptible Patients. The detection of patients susceptible to malignant hyperthermia prior to surgery is quite difficult. A family history, when present, is the most obvious clue. It is important to realize, however, that a negative family history and even prior uneventful surgery on a patient does not rule out malignant hyperthermia, since this condition depends on the anesthetic used and its dose. Some susceptible patients present with muscle abnormalities characterized by a general increase in muscle bulk and strength combined with localized muscle weakness (3). Abnormalities of the back muscles may lead to mild scoliosis, lumbar lordosis, and winged scapula. Various hernias may also be present. The serum CPK is a useful diagnostic indicator, but it is neither specific nor sensitive. A variety of factors, including emotional stress, exercise, medications, and recent muscle injury, may increase CPK. Furthermore, approximately one-third of patients susceptible to malignant hyperthermia have normal CPKs. The most accurate means of diagnosing susceptibility is a skeletal muscle biopsy. The muscle fibers are subjected to immersion in increasing concentrations of caffeine and caffeine-plus-halothane. In such mediums, the muscle fibers of malignant-hyperthermic-susceptible patients undergo contraction, while the muscle fibers of nonsusceptibles do not. In addition, muscle biopsies in known cases of malignant hyperthermia also show depressed calcium uptake and abnormally low myofibrillar calcium-dependent ATPase activity (8).

Procedures with Known Sufferers. For a patient with known malignant hyperthermia, surgery should be performed only if absolutely indicated. In this case volatile inhalational agents, depolarizing muscle relaxants, and amide-type local anesthetics must be avoided. Barbiturates, tranquilizers, narcotics, and ester-derivative local anesthetics are relatively safe. Mild sedatives should be given preoperatively so as to minimize emotional stress, which many authors believe is clearly linked to the syndrome (12). For three days prior to surgery, an adult should receive dantrolene sodium, 100 mg four times a day, and a child should receive 2.2 mg/kg daily in four divided doses. In addition, a large-gauge intravenous catheter should be inserted into a peripheral vein, and Ringers lactate should be infused at a rate of 2 ml/kg/hr. On arrival at the operating room, temperature probes should be inserted in the patient's axilla and rectum, the vocal cords sprayed with 5% cocaine, and intubation accomplished without a muscle relaxant. Thereafter, an arterial catheter, a CVP monitor, and a Foley catheter should be inserted. Anesthesia time should be as brief as possible, and the patient should be closely monitored for at least four hours postoperatively. Routine chemistries should be obtained in the recovery room and for at least four days subsequently. Dantrolene is to be continued for the first three postoperative days (11).

Summary

Malignant hyperthermic crises have been occurring ever since general anesthetic agents were discovered, but it was not until 1962 that these crises were recognized as being due to a familial muscle disease. Denborough's description of malignant hyperthermia in a 21-year-old male spurred interest in the disease entity, its pathogenesis, and its treatment. Malignant hyperthermia is inherited in an autosomal dominant fashion with reduced penetrance and variable expressivity. The precise site and nature of the muscle abnormality is unknown, but the symptomatology is secondary to increased intracellular concentrations of calcium. The porcine model of malignant hyperthermia was instrumental in the discovery that dantrolene controls the syndrome. Marketed since 1980, dantrolene sodium is the treatment of choice for this condition. Ongoing research in this field is directed at ascertaining the exact abnormality and in developing an inexpensive, sensitive, and specific screening test.

Acknowledgments

Special thanks to Robert S. Hyman, M.D., Assistant Clinical Professor of Orthopaedics, Mount Sinai School of Medicine.

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Submitted for publication May 1982.

Left to right: Dr. Gordon Oppenheimer, Dr. Burrill Crohn, and Dr. Leon Ginzburg. (*Courtesy of Dr. Henry D. Janowitz.*)

Introduction

The year 1982 marked the fiftieth anniversary of the publication of the hallmark paper "Regional Ileitis" by Drs. Burrill Crohn, Leon Ginzburg, and Gordon Oppenheimer. This publication marked the beginning of an era of intense study of inflammatory bowel disease at The Mount Sinai Medical Center.

Dr. Henry Janowitz and I felt that in recognition of the occasion, a major symposium should be presented reviewing all aspects of inflammatory bowel disease. It was our concept that the material presented be the work done at Mount Sinai by our colleagues over the years. We realized however that in order to provide an appropriate balance, several experts in the field should be invited to comment, critique, stimulate, and lead discussion.

We were most fortunate that Dr. John E. Lennard-Jones, Professor of Gastroenterology at London Hospital Medical Center and Consultant in Gastroenterology at St. Mark's Hospital, London, Mr. John Alexander-Williams, Chairman of the Department of Surgery of The General Hospital, Birmingham, England, and Dr. Fred Kern, Jr., Professor of Medicine and Head of the Division of Gastroenterology of the University of Colorado School of Medicine, consented to join us in this venture. In addition, Drs. Burton I. Korelitz and Arthur E. Lindner, though no longer on our faculty, returned to review developments in their areas of expertise; work that had begun while they were with us. We were most pleased that Dr. Crohn, now 98 years of age, was able to appear at the conference to be recognized. In addition, Dr. Leon Ginzburg was present for every session, commented regularly, and enabled us to put much of the material in its proper historical perspective.

The symposium was organized into five major sections:

1. The evolution of our understanding of Crohn's disease.
2. Pathophysiologic consequences of ileitis and colitis.
3. Therapeutic approaches to inflammatory bowel disease.
4. The search for etiologies.
5. The psychosocial impact of inflammatory bowel disease.

The final hour was devoted to "The Next Fifty Years"; this discussion was moderated by Dr. Kern and consisted of a panel of Mr. Alexander-Williams, Dr. Janowitz, Dr. Kern, Dr. Lennard-Jones, and myself. Each section was followed by a question-and-answer and discussion period.

This issue of *The Mount Sinai Journal of Medicine* presents the symposium almost in its entirety. The talks and discussions were taped, transcribed, and then edited by the authors. Several participants submitted manuscripts in advance, but these are almost a verbatim reproduction of their talks.

What follows therefore is a very personal account of the work done in the field by a group of physicians who have dedicated their professional lives to the study of inflammatory bowel disease.

I feel privileged to have had the opportunity to collate this material. I am most appreciative of the participation of all of the authors and our invited guests. I want to especially thank Henry Janowitz for his cosponsorship of this project and David A. Dreiling, Editor of the *Journal*, for agreeing to publish this special issue.

ARTHUR H. AUFSES, JR., M.D.
Guest Editor
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The Mount Sinai Journal of Medicine
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Remarks: A Historical Perspective

Leon Ginzburg, M.D.

Although he was not listed on the formal program, the organizers of the symposium asked Dr. Leon Ginzburg to make a few remarks. This he did, to the education and delight of all present. Dr. Ginzburg's talk was presented during the first morning session, moderated by Dr. John E. Lennard-Jones. What follows is a distillation of Dr. Ginzburg's comments and Dr. Lennard-Jones' acknowledgment. I believe these few pages will be helpful in viewing the historical perspective of granulomatous inflammatory bowel disease.—Editor

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Dr. Leon Ginzburg: I have been asked to speak for five minutes. That's like trying to dam up Niagara Falls after five minutes, but I'll try. People very frequently ask: "How did you people come to study this disease? Obviously, it wasn't very well known." In 1933, Dr. Oppenheimer and I published a paper entitled "Nonspecific granulomata of the intestines (inflammatory tumors and strictures of the bowel)" in *Annals of Surgery*. The paper was from the surgical service of Dr. A. A. Berg and the Department of Laboratories of The Mount Sinai Hospital. This paper was originally presented for publication at the same time as the paper in 1932, but it was 50 pages long and we couldn't get it printed in a surgical journal, so we shortened it by about one third.

[A footnote to the title in the original article states: "Presented before the American Gastro-Enterological Association in May, 1932. The section on localized ileitis represents a joint study with Dr. Burrill B. Crohn." May 1932 was the same month in which Dr. Crohn presented his paper at the meeting of the American Medical Association.—Editor]

We were clinically observing patients with abdominal masses, with obstruction, which were being wrongly diagnosed as tuberculosis or carcinoma. Wrong prognoses were given and too much surgery was being done at some times, too little at others. There were 52 cases in all. We eliminated several cases involving the jejunum because we didn't have enough information, and we eliminated cases involving the rectum since we were able to diagnose rectal disease with sigmoidoscopy and biopsy.

The 52 patients were divided into six groups, with some overlap. The first group consisted of patients with extra- or peri-intestinal granulomata secondary to sealed-off perforations of the bowel. I originally encountered these in 1927. Some were patients of Dr. Berg. In some of these we found perforations due to fishbones and toothpicks, around which had formed large inflammatory masses.

Then, in 1928, I published the paper "Granulomata secondary to known vascular disturbances of the gut." Most of these cases were patients who had strangulated hernias in which the bowel was affected but was considered viable. Anywhere from a few weeks to two months later, these patients would return with obstruction due to either an annular or segmental stricture of the bowel.

The third group of cases was called localized, hypertrophic, ulcerative stenosis of the terminal ileum. In our study of the pathology, which was monitored by Dr. Paul Klemperer, chief of pathology at the time, we pointed out the fact that there were skip lesions, and that we could not find any caseation in the tuberclelike structures. We never could find tubercle bacilli; in about six cases, we injected fresh tissue into rabbits, guinea pigs, and chickens but could never reproduce tuberculosis. We concluded that the primary lesions were lenticular or ovoid ulcerations along the mesenteric side of the bowel. We also noted that perforations of the ulcers usually occurred in between the leaves of the mesentery, and at that time perforation into the free peritoneal cavity was rather rare. Whether free perforation is related to steroid therapy has not been settled, but certainly there was no steroid therapy in the 1920s. We also showed that this disease was not related to appendicitis, because we found distal granulomatous ileitis with a normal appendix. We also advanced a theory that the giant cells in the pseudotubercles were perhaps not an intrinsic part of the disease, but were perhaps due to the fact that vegetable cells had entered the lymphatics and at times were even carried to the lymph glands.

The fourth group that we presented we called localized hypertrophic colitis. Here is a slide of an x-ray taken in 1925, showing obvious involvement of the ascending colon and hepatic flexure, extending into the transverse colon. This next picture is of the resection specimen, and you can see a fairly advanced case of granulomatous disease of the bowel. There are several large ulcers and a lot of small ulcers, between which the mucosa is hypertrophied and edematous, and there are areas of normal bowel. The patient returned in 1928, three years later, with what we call recurrent disease. As you can see from the picture, it should actually be called progression, since the disease now extends into the transverse colon as far as the splenic flexure. The patient refused further surgery, and we lost track of him. In that group we reported five cases in the right colon, three cases at the junction of the descending colon and sigmoid, and three in the sigmoid.

I could go on, but I have only five minutes. Thank you.

[In the article by Drs. Ginzburg and Oppenheimer, the other two categories described were cases of "simple penetrating ulcers of the colon" and "lesions secondary to inflammation of the appendages of the bowel such as appendicitis, diverticulitis, typhlitis."—EDITOR]

Dr. Lennard-Jones: Thank you very much indeed, Dr. Ginzburg. I think that medical history is a very fascinating, humbling subject. It's been said that there is nothing new under the sun, and we keep rediscovering things that have been discovered before. But, perhaps, in a way, medical research is not a circle, but more like a spiral. We go round and round, but we make a little progress, and perhaps during this symposium we will make just a little more progress. I was interested that Dr. Ginzburg had tried some transmission experiments in the late 1920s. Tomorrow we are going to hear about transmission experiments in the 1970s, and so we go round. Thank you again.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Overview: The Road to Crohn's Disease

HENRY D. JANOWITZ, M.D.

I have been asked to give a brief overview of the evolution of our understanding of inflammatory bowel diseases, but this entire symposium is itself an overview. We are delighted that not only our foreign visitors but our alumni are joining us for it. The title of my talk—without any apologies to Bob Hope—is "The Road to Crohn's Disease." And it is most appropriate that for my title, I have borrowed from Leon Ginzburg's paper, "The Road to Regional Enteritis," which he published in *The Mount Sinai Journal of Medicine* in the year 1974. All of you here recognize that the term Crohn's disease is a shorthand notation for the entire disease spectrum which he, Burrill Crohn, and Gordon Oppenheimer first described in its ileal component. I think no more need be said about this aspect in this conference.

What was the road before Crohn, Ginzburg, and Oppenheimer? In retrospect, the evolution of our understanding of a disease process often seems to be a slow steady accumulation of information. The road appears straightforward. However, somewhere on the path there occurs a quantum leap. I have found an early case in Wilks and Moxon, *Textbook and Lectures of Pathological Anatomy* (1875). The authors describe a young man who had a lesion of the ileum which was so narrow that a quill could not be passed through it; this is in the midst of their classical description of ulcerative colitis, which is ascribed to them. Braun described several cases of nonspecific inflammation of the small bowel in the German literature in 1904. Our British colleagues have lately put forth the strong case that Dalziel, a Scottish surgeon, in 1913 described six cases in detail, treated surgically; in retrospect I think these cases fit the entity we are discussing, and from which tuberculosis had been clearly and carefully excluded. Wilensky and Moschowitz, colleagues here at Mount Sinai, in 1923 reported on granulomatous lesions of the small bowel from the same pathology laboratory that Ginzburg and Oppenheimer were working in at the time. The cases were falling together. However, the paper we are celebrating was a quantum leap. Its 14 cases had a critical mass which set off a chain reaction which has never stopped.

I want to make only three points in my discussion on the evolution of our knowledge of this disorder: first, the recognition that this is a new disease, and one of increasing incidence. Second, I want to comment on the development of our understanding that this is a disorder that may involve the entire gastrointestinal tract and even overflow. And third, I shall briefly discuss the recognition of the consequences of the primary intestinal disease, the recognition that the remainder of the human organism reacts to the deleterious effects of the primary disease, based in part on the disturbance of the pathophysiology of the gastrointestinal tract.

A New Disease. I have made the point elsewhere and I would like to repeat it: I think this is a new disease. I really cannot conceive that the great nineteenth-century pathologists of the German and Viennese school, Virchow, Cohnheim, et al, who made careful runthroughs of the entire small bowel in all of their autopsies, would have missed it. And they certainly would have separated it from acid-fast disease. Remember, the few precursor papers I have cited occurred after the turn of the century. Indeed, in their paper of 1923, Wilensky and Moschowitz commented on the fact that not much had been written about this disease until the early 1900s. By the time the colleagues at Mount Sinai had assembled their cases, Bargen had collected his group of patients at the Mayo Clinic. Indeed it is thought that they may be the same patients, because patients in New York were in the habit of commuting to Rochester, Minn. frequently in those days. But certainly after 1932 came the deluge. Further, I think it is clear now that the increasing incidence is not merely a function of earlier recog-

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nition. In such countries as the Scandinavian and in Great Britain, where accurate health records exist, the incidence is increasing or is approaching a peak, if it has not already peaked. It is certainly spreading far beyond the original Jewish population reported in the original paper from this institution.

Sites and Involvement. Although Crohn's disease is essentially a disease of the distal gastrointestinal tract (interestingly, it focuses behind the ileocecal valve and behind the rectal sphincters), investigators promptly learned that in addition to the ileum, the jejunum could also be involved. I think the following year the Mayo Clinic finally got a chance to put its cases on record, and Bargen and his colleagues described that. A year later, Ralph Colp, then a Mount Sinai Hospital surgeon, described a case with a fistula into the cecum. Very shortly after that Abe Penner, with Burrill Crohn, described the characteristic perirectal disease. Soon the duodenum and stomach were added to the list of affected areas. It is difficult to prove that the esophagus is the site of this disease and this must have some interesting pathogenetic bearing, in keeping with my idea that some factor accumulates behind areas of stasis; but involvement of the mouth and lips, of course, has clearly been documented.

Arthur Lindner, a Mount Sinai alumnus and now associate dean at New York University, discusses the recognition of Crohn's disease of the colon elsewhere in this symposium. I want to comment on one aspect of this briefly. Richard Marshak had for a long time been pointing out that regional enteritis could overflow into the colon, and the first detailed radiographic papers on granulomatous colitis came from Mount Sinai (those of Marshak, Lindner, and the late Bernie Wolf). The Gastroenterology Division joined Dr. Marshak in what was probably the first paper on this side of the Atlantic. Mount Sinai was, it must be confessed, slow to appreciate this facet. In England, even before Lockhart-Mummery and Basil Morson, Wells and Brian Brooke had long been talking about granulomatous colitis and I think that the concepts of our pathologic heritage at Mount Sinai tended to force Crohn's disease, or Crohn, Ginzburg, and Oppenheimer's disease, to stay north of the ileocecal valve and to separate it from ulcerative colitis. However slow in getting started at first, I think the paper in the *New England Journal of Medicine* in 1963 loosed the floods, at least on this side of the Atlantic.

Indeed I have the impression that now, if the clinical and radiographic pictures are not that of classical ulcerative colitis, and if the bacteriologic studies are negative, we are forcing every acute form of colitis that is not transient or acutely self-limited into the category of granulomatous (Crohn's) disease. There must be other, a hundred other, inflammatory disorders of the colon which we have not yet sorted out. In our enthusiasm to put granulomatous colitis on the map, we should be a bit more restrained in trying to fit every disease into this Procrustean bed.

And finally this gastrointestinal disorder can overflow the gut. It can spill over into the larynx, and at Mount Sinai we have on occasion seen metastatic disease—lesions of the skin, not pyoderma gangrenosum or erythema multiforme or erythema nodosum, and not related to fistulae, but metastatic from elsewhere. One begins to get the feeling that although the gut is the primary seat of this disease, it may be more widely disseminated.

Impact on the Organism. Parallelling the explosion of information on the natural history of this disorder has been the recognition of the impact of this disease on the rest of the organism. Daniel Present details these extraintestinal manifestations in another article. I want to sketch here the leading concepts in which Mount Sinai has played some part in what I think are classic contributions. A whole host of extraintestinal disease manifestations which at present are postulated to be of immune origin involve the anterior chamber of the eye, the mouth, the peripheral joints, and the florid destructive lesions of the skin. Other participants in this symposium discuss the large group of secondary manifestations of this disease which are the result of disturbance of the pathophysiology of the bowel itself: gallstones with diminished bile salt pool, malabsorption and steatorrhea; those fascinating renal complications of uric acid stones and the anomaly of hyperoxaluria with renal oxalate stones; the recognition by our predecessors at this hospital, continued by Daniel Present, of the noncalculous hydronephrosis which is part and parcel of this disease; together with the increasing recognition of amyloid. At Mount Sinai we have several patients with renal amyloid whom we are now treating with colchicine, as familial Mediterranean fever is treated. So this symposium detailing the contributions of Mount Sinai investigators so far will I think also demonstrate that Mount Sinai has not lost any of its momentum in traveling the road to the therapeutic solution of these devastating inflammatory bowel diseases

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Recognizing Crohn's Disease of the Colon

ARTHUR E. LINDNER, M.D.

Abstract

In Crohn's disease that exclusively or predominantly involves the colon, characteristic findings include a history of bloodless diarrhea, a normal proctoscopy examination or patchy rectal mucosal lesions, and anal disease. The terminal ileum is frequently involved as well as the colon. The distribution of disease in the colon is often segmental and right-sided. Differential diagnosis includes ulcerative colitis, infectious diarrheas, tuberculosis, radiation enteritis, ischemia of the bowel, and scirrhous carcinoma.

It is surely a sign of medical progress that we can now confront the differential diagnosis of Crohn's colitis without questioning its existence. Only for a bit more than two decades has Crohn's disease been generally acknowledged as a cause of chronic inflammatory disease of the colon (1–3).

The first observation to make about Crohn's disease of the colon is that it is uncommon—at least when only the large intestine is involved. Most Crohn's colitis is really ileocolitis. It is difficult to get precise figures from the large reported series, but the proportion of patients with Crohn's disease who have exclusively colonic involvement ranges from 12% reported from this institution (4) to approximately 33%. The number I carry around in my head is that perhaps 15% of Crohn's disease is confined to the colon.

On the other hand, colonic involvement of some degree is frequent in Crohn's disease. An approximation might be that two thirds of all patients with Crohn's disease have some involvement of the colon.

Such considerations become very practical when one seeks clinical information concerning Crohn's disease of any specific part of the gut. Here, for example, we're concerned with the colon. Are we talking about disease confined to the colon, disease that predominantly involves the colon, or disease that simply includes any portion of the colon in its distribution? Often these distinctions are not made, so assessments from the literature can be difficult and statistical analyses confusing. I think there is a welcome place in the literature for a good current study that simply records and follows the distribution of Crohn's disease within the intestinal tract in a large group of patients, using modern diagnostic techniques and awareness.

I concentrate here on Crohn's disease predominantly or exclusively involving the colon.

As clinicians we recognize that Crohn's disease may affect all of the colon, but often it is segmental, and any part of the large bowel may be the site of disease. There is a tendency for the right side of the colon and the transverse colon to be affected, usually in association with concomitant disease in the ileum, and there is a tendency to spare the rectum. Disease of the anus is common indeed, perhaps in three-fourths of patients with colonic disease, and when the rectum is involved, anal lesions are almost always present (5). These lesions of the anus include edematous skin tags, fissures, ulcers, abscesses, and fistulas.

Usually the distribution of disease in the colon can readily be appreciated on barium enema examination, but even here there may be uncertainties. The familiar and characteristic x-ray features of Crohn's disease are reviewed below by Richard Marshak, but some-

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times only aphthous ulcers, identified by double-contrast barium enema, mark the colonic involvement. This special technique is necessary when the extent of disease is clinically relevant and important (6, 7). Histologically, even the normal rectum may not really be normal. The group at Lenox Hill Hospital (8, 9) has pointed to the presence of microgranulomas and other histological abnormalities in otherwise normal rectal mucosa on biopsy. The implications of these findings remain to be assessed.

The pathology (10) of Crohn's disease of the colon, briefly summarized, is transmural inflammation, especially submucosal in its distribution, with relatively uninvolved mucosa. Aphthous ulcers and submucosal nodules are early findings. Later in the spectrum of disease, linear ulcers and transverse fissures are found, forming the well-known cobblestone mucosa. Internal fistulas occur, but they derive more often from areas of small bowel disease than from the colon. Granulomas are the histological hallmark but pathologists report granulomas in only about half the surgical specimens of Crohn's disease.

Crohn's colitis may occur in any age group from nursery school to the senior citizens' club. But the typical patient (11), male or female, is in the late teens or early twenties. The onset of the disease is sometimes slow and quite insidious, unlike the usually rapid development of symptoms in ulcerative colitis. Abdominal cramps and weight loss are regular findings. Frequent formed stools may progress to a loose diarrhea. Gross blood in the stool is uncommon unless the rectum is diseased. This observation probably reflects the relative absence of mucosal inflammation in the transmural process. Anal lesions are often present, even as the earliest manifestation of the disease, and painful aphthous ulcers of the mouth may be found when colitis is active.

A galaxy of extraintestinal manifestations of Crohn's colitis have been described. These include erythema nodosum and pyoderma gangrenosum, peripheral arthralgia, and arthritis, and in the liver, pericholangitis and sclerosing cholangitis. Uveitis (13) and ankylosing spondylitis (14) have attracted particular interest because their strong association with the HLA-B27 histocompatibility antigen suggests genetic implications for those patients with Crohn's disease who exhibit these associated manifestations.

The diagnosis of Crohn's colitis can usually be made by the history and sometimes the physical findings of anal disease or the right lower quadrant mass of ileocecal disease. Sigmoidoscopy findings are often normal. When the rectum is affected, findings tend to be patchy, segmental ulcerations with surrounding edema, rather than the diffuse friability we associate with ulcerative colitis. Biopsy may reveal histological confirmatory findings of Crohn's disease to the pathologist, including—with luck—granulomas.

Stool specimens should be examined to exclude infectious agents.

Barium enema examination often yields characteristic findings, and small bowel x-rays demonstrate the ileal component of ileocolitis. In a confusing situation, colonoscopy (15) may be of help when mucosal changes are minimal.

There is a differential diagnosis to be considered for the several manifestations and distributions of Crohn's colitis. In an acute episode, *Yersinia* infection (16) may mimic ileocolitis, and *Shigella* and *Campylobacter* (17) infections sometimes resemble acute Crohn's disease. It is possible that the toxin of *Clostridium difficile* may be associated with acute exacerbations of previously stable disease (18).

More chronic aspects of Crohn's disease are mimicked by amebiasis, ileocecal tuberculosis, radiation enteritis, ischemia of the bowel, and scirrhous carcinoma (19). Sigmoid diverticulitis sometimes resembles segmental Crohn's disease and, to compound the confusion, both diseases may exhibit long sinus tracts (20).

The principal differential diagnosis is with ulcerative colitis (21), and here the evidence favoring Crohn's disease includes bloodless diarrhea, normal sigmoidoscopy findings, anal lesions, and involvement of the terminal ileum.

We must acknowledge that not all colitis can be classified with certainty at the present time, no matter how thoughtful and complete the evaluation (22). Followup does often help in providing a diagnosis when an initial study is confusing. Nevertheless, a favorite current figure is that in perhaps 15% of patients with chronic inflammatory disease limited to the colon a firm diagnosis cannot be established. We can hope that improved diagnostic techniques in the years ahead will help to reduce that number.

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The Mount Sinai Journal of Medicine
Vol. 50, No. 2, March-April, 1983
Printed in U.S.A.

The Roentgenologic Contribution

Richard H. Marshak, M.D.,† and Daniel Maklansky, M.D.

It is appropriate that our topic is "The roentgenologic contribution." Among the many contributions that Richard Marshak made to radiology, one of the most significant is the role he played in the radiologic descriptions of Crohn's disease in the stomach, duodenum, small bowel, and colon. Dr. Marshak joined Dr. Crohn in his office as consulting radiologist in 1946. Utilizing Dr. Crohn's extensive clinical material, he had the opportunity to review thousands of cases of inflammatory bowel disease. The publicity attendant on the disclosure that President Eisenhower was operated on for ileitis in 1955 brought many more people to consultation with Drs. Crohn and Marshak. By reviewing this extensive experience, Dr. Marshak was able to present an accurate, sequential description of the radiologic pattern of Crohn's disease and its progression. He established criteria to identify the extent, the location, the nature, and the severity of the disease. In effect, he offered a radiographic natural history of Crohn's disease by distinguishing between the early nonstenotic and the later stenotic phases of the disease.

In this brief report we review the radiologic history of Crohn's colitis and Dr. Marshak's involvement in the organization of this data.

The earliest roentgen findings in the nonstenotic phase of Crohn's disease are tiny aphthous ulcerations. These then coalesce and advance to larger punched-out and serpiginous ulcers in association with thickening and blunting of the mucosal folds. These longitudinal and transverse ulcerations combine to form the familiar cobblestone pattern. As the mucosa is denuded by the ulcerations, there is an attempt at healing which results in fibrosis, ultimately leading to the stricture formation that is seen in later stages of Crohn's disease.

Radiologic Natural History of Crohn's Colitis

The following points summarize the roentgenologic findings in granulomatous colitis (1):

1. Tiny discrete superficial ulcers (aphthoid ulcers) usually associated with small, radiolucent nodules.
2. Segmental distribution, more disease on right than on left.
3. Universal distribution in colon almost always associated with involvement of terminal ileum.
4. Nodular, irregular pattern after evacuation.
5. Punched-out ulcers; small or large; smooth or irregular.
6. Longitudinal and transverse ulcerations.
7. Combination of transverse and longitudinal ulcerations with cobblestoning.
8. Strictures.
9. Irregularity of contour with asymmetric involvement and pseudodiverticula.
10. Skip lesions.
11. Fistulas, frequent in ileum, considerably less common in colon.
12. Intramural abscesses.

Figure 1 illustrates the earliest roentgenologic findings in Crohn's disease: aphthous ulcers. These are best seen on air contrast studies. Pathologically and endoscopically, these aphthoid ulcers are small ulcer craters measuring 1–4 mm in diameter, surrounded by a radiolucent halo representing edema of the adjacent mucosa. Aphthoid ulcers are not pathognomonic for Crohn's disease and may occur in any acute or early inflammatory process, including amebiasis, shigellosis, herpes, and Bechet's syndrome. The presence of aphthous ulcers alone without other characteristic findings of Crohn's disease is insufficient to establish an unequivocal diagnosis of granulomatous colitis. We have yet to see a documented case in which the radiographic or endoscopic

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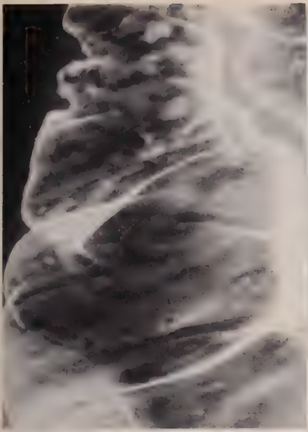

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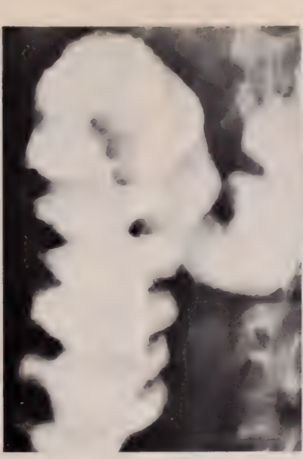

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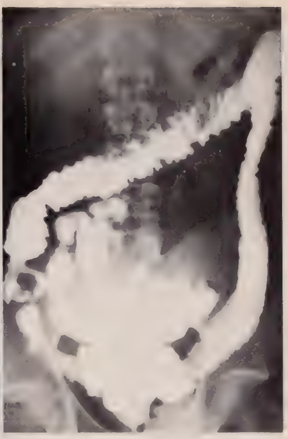

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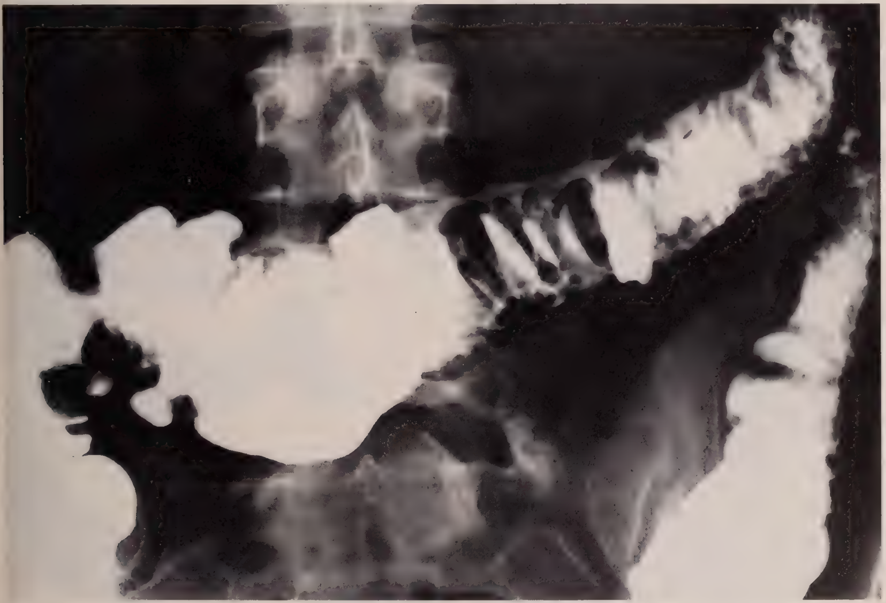
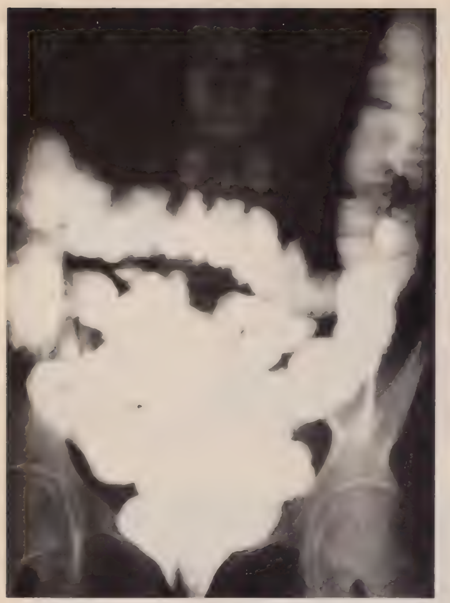


FIG. 4.

findings were solely those of aphthous ulcers which then progressed to classic Crohn's colitis. Tiny ulcerations can also be seen utilizing the conventional barium enema with full barium column; they appear as small projections from the contours of the bowel, as in Figure 2. Note also the accompanying edema of the adjacent mucosa characterized by thickening of the haustral folds as well as small contour defects along the inferior surface of the transverse



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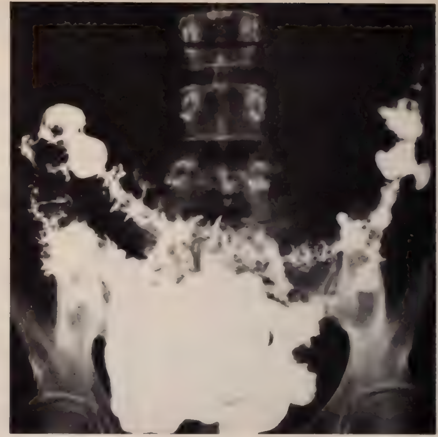

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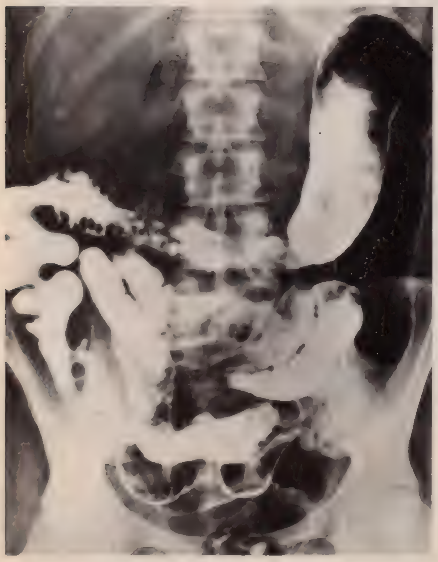

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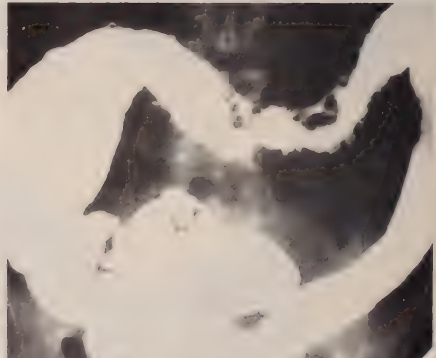

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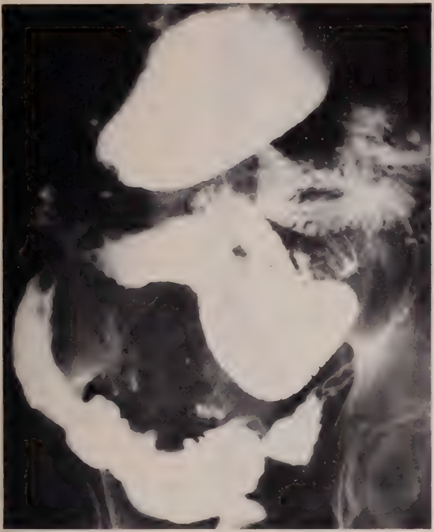


FIG. 9.

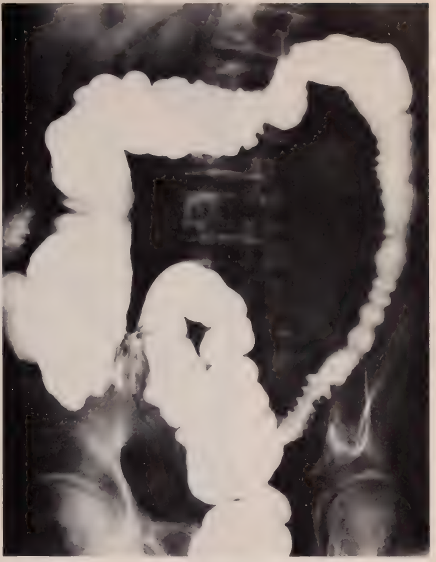
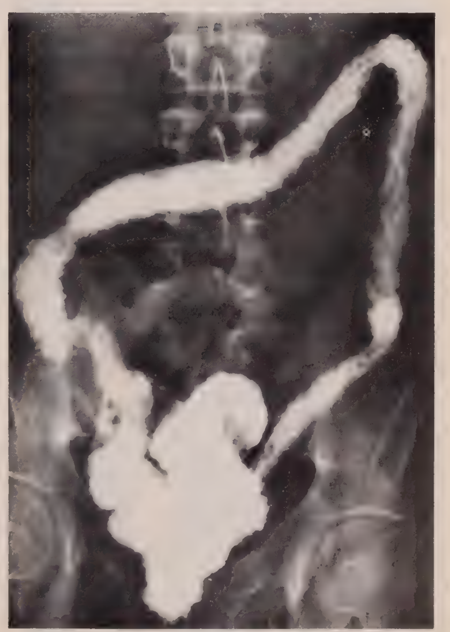


FIG. 10.

colon. An ulcer niche is seen to project from the center of each defect. These defects represent edema of the mucosa. The small ulcer niche represents a tiny ulcer seen in profile, rather than *en face* as in Figure 1.

Figure 3 illustrates the progression of these small ulcerations to larger punched-out ulcerations which project from the contour of the sigmoid colon and transverse colon. The usual distribution of Crohn's ileocolitis is evident—involvement of the right side of the colon and distal ileum. As these ulcerations become deeper they tend to coalesce in both the longitudinal and transverse axes of the bowel, resulting in characteristic longitudinal and transverse ulcerations. These are identified in the distal transverse colon in Figure 4. The mucosa between the ulcers is edematous.

We have found postevacuation studies in the conventional barium enema to be extremely valuable in assessing the extent and severity of Crohn's disease. As illustrated in Figure 5, the filled colon demonstrates only slight changes, characterized by narrowing and rigidity of the distal transverse colon and proximal descending colon in association with slight irregularity of the haustral pattern. A postevacuation film of the same examination (Figure 6) reveals considerable irregularity of the mucosa of the



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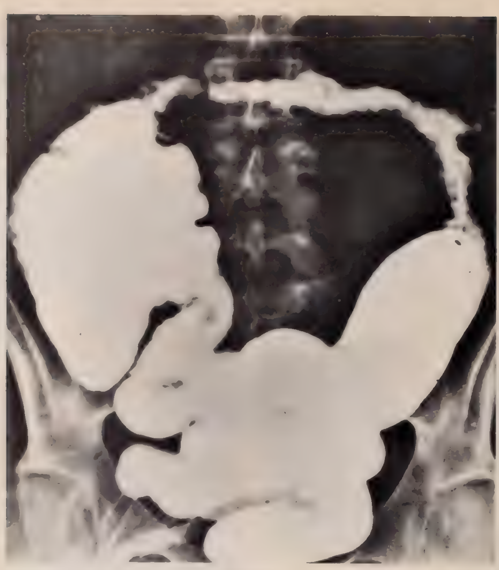

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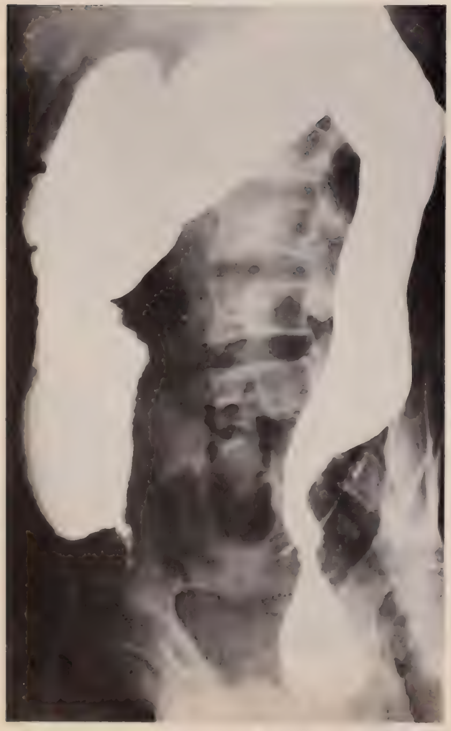

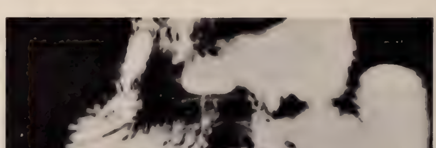

FIG. 13. *Left.*
FIG. 14. *Right.*

ascending, transverse, and proximal descending colon. The irregular mucosa has assumed a knotted-rope or cobblestone appearance. Several large pseudodiverticula are identified in the left side of the colon. Pseudodiverticula represent localized skip lesions and are caused by eccentric involvement of the wall of the bowel by granulomatous disease. Those portions of the circumference of the bowel which are free of fibrosis, lymphagectasia, and ulceration of mucosa maintain their elasticity and are able to bulge outward with the barium column.

The classic radiographic presentation is seen in Figure 7. Ileocolitis of moderate severity involves the distal 6–8 inches of ileum and the ascending colon and transverse colon. These findings are marked by rigidity, narrowing, and longitudinal and transverse ulcerations. The combination of longitudinal and transverse ulcerations in the proximal transverse colon causes the intervening inflamed mucosa to become compartmentalized and project as nodular defects or cobblestones. Several of the transverse ulcerations are deep and are seen to project cephalad from the superior border of the transverse colon. A small fistulous tract between the distal ileum and the adjacent cecum is also characteristic. Narrowing of the cecum produces a cone shape. The cone-shaped cecum is more common in ileitis than in tuberculosis or amebiasis.

Ulcerations in Crohn's disease may be bizzare and stellate, as in the distal transverse colon with deep punched-out and stellate ulcerations in Figure 8. Almost the entire colon is involved, with a skip lesion in the splenic flexure. Haustra markings are absent. The rectum is spared. The deep ulcers may eventually penetrate through the wall of the bowel and form fistulous tracts to adjacent organs. Figure 9 illustrates such a case. Involvement of the colon with Crohn's disease results in a gastrojejunocolic fistula.

Fistulas are not unusual in Crohn's colitis. In Figure 10 a sigmoid ileocecal fistula is identified in a patient with Crohn's disease of the ileum and right colon—in effect, a short-circuiting.

The differentiation between Crohn's disease and ulcerative colitis is not difficult in 90%–95% of cases. However, when the entire colon is involved with Crohn's disease, difficulty may be encountered in differentiating between the two diseases. When there is concomitant disease involving the terminal ileum, as illustrated in Figure 11, the diagnosis of Crohn's disease is apparent.

Strictures are not infrequent complications of Crohn's disease. These are usually multiple, but single strictures may present diagnostic problems. Figure 12 represents stricture formation with pseudodiverticula and skip lesions in a case of Crohn's disease. Figure 13 illustrates a moderately severe stricture in the distal descending colon associated with several fistulous tracts.

Unlike ulcerative colitis, total colectomy in Crohn's colitis may not be curative. When disease recurs in the new ileum proximal to the ileostomy, the disease is identical to regional ileitis and is characterized by spasm, irritability, ulceration, rigidity, and narrowing (see Figure 14).

In summary: the radiologic features characteristic of granulomatous colitis are those that have been identified in the small bowel in patients with regional enteritis. These include tiny ulcers (aphthae), punched-out ulcers, small nodular defects, skip lesions, contour defects, longitudinal ulcers, transverse fissures, deep and ragged ulcers (abscesses), eccentric involvement, pseudodiverticula, narrowing and stricture formation, pseudopolypoid changes with a coarse and cobblestonelike mucosal pattern, sinus tract, and fistulas. One of the striking radiologic features of granulomatous colitis is the frequency of concomitant and similar disease in the small bowel. Eighty-five percent of the patients studied who have granulomatous colitis also have disease involving the ileum. In 15% the disease is confined to the large bowel.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Perspectives from Abroad

JOHN E. LENNARD-JONES, M.D., FRCP

The eponym Crohn's disease is succinct but reveals our inability to define the condition in terms of etiology or pathogenesis. The achievement of Crohn and his colleagues was to separate a small homogeneous group of patients with terminal ileal disease from a much larger heterogeneous group of patients with nonspecific inflammations of the gut. As time has passed, more and more disorders from the heterogeneous group have been included under the general term "Crohn's disease," so that now inflammations with the histological characteristics associated with the ileal lesion have been described from all parts of the gastrointestinal tract, the lip and mouth, the anus, and also from such diverse sites as the skin, liver, muscle, and bone.

Epidemiology of Crohn's Disease

It seems certain that the prevalence of Crohn's disease is greater in Europe and North America than in Africa, the Middle or Far East, or South America. Good epidemiological data tends to be lacking in areas where the prevalence is probably low, but the relative paucity of reports from experienced clinicians is convincing (1).

In some areas of Europe with relatively static populations and good centralized clinical records, it has been possible to work out changes in incidence with time. All such studies have shown a steadily increasing incidence of all forms of Crohn's disease, an increase that cannot be entirely ascribed to better diagnostic methods or altered diagnostic criteria. A representative series showing numbers of new cases diagnosed in an urban area of Wales is shown in Figure 1, which provides data from 1934 to 1980 (2). In Britain and Sweden the annual incidence of new cases of Crohn's disease now approximates to 5 per 100,000 per year (3–5). A little evidence is now accumulating that the rise in incidence over the years may have reached a plateau at around this figure.

If the incidence of Crohn's disease has increased so markedly in Europe, why has it? It is tempting to ascribe the increase to an environmental factor. The epidemiological trends in Europe and developing countries may yet shed light on etiology. Are we about to see a worldwide spread of the disease, and if so why?

Definition and Diagnosis of Crohn's Disease

Workers in Europe have taken a particular interest in numerical methods of classifying inflammatory bowel disease. One technique, termed numerical taxonomy or cluster analysis, demonstrated the relative homogeneity of the disorder we call ulcerative colitis and the heterogeneity of the condition we term Crohn's colitis (6). Similar evidence was derived from analysis of discriminant patterns; patients with Crohn's disease fell into a variety of patterns, whereas patients with ulcerative colitis fell into one pattern (7).

No biochemical, immunological, or microbiological technique has so far contributed to the definition of Crohn's disease, and diagnosis is still based on anatomical description. Unfortunately, no defining feature has been recognized which is present in every patient regarded as suffering from the disease and absent in all other disorders. The noncaseating epithelioid granuloma is of particular importance because it is relatively common in Crohn's disease and rare in other conditions. However, it must be recognized that whereas the granuloma tends to be regarded as an anatomical marker, it is really a visible manifestation of mononuclear metabolic activity.

A scoring system for the diagnosis of Crohn's disease has been suggested (8, 9) using macroscopic and microscopic anatomy as criteria, detailed below.

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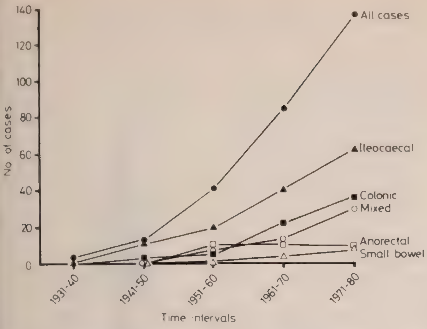

FIG. 1. Number of new cases of Crohn's disease in an urban area of Wales, 1934–1980. From Harries et al (2).

Macroscopic Anatomy:

- A predilection for involvement of the **terminal ileum** with ulceration of the mucosa and narrowing of the lumen due to swelling of the mucosa and thickening of the intestinal wall.
- A tendency to development of a chronic **anal lesion,** often with ulceration of the anal canal and/or perianal skin, swelling of the skin to form edematous tags, sepsis and fistula formation.
- **Fistulae** between the inflamed gut and other hollow viscera or the skin surface.
- **Discontinuity** of inflammation along and around the circumference of the gut anywhere between lip and anus.
- Cleftlike ulcers or **fissures** passing perpendicularly from the intestinal lumen into the gut wall.

Microscopic Anatomy:

- **Epithelioid granulomas,** without caseation, and often with Langhans-type giant cells.
- **Lymphoid aggregates** throughout the thickness of the bowel wall.
- **Normal epithelial** mucus content in the presence of acute inflammation. Inflammation involving **all layers** of the gut wall (transmural).
- **Fissuring ulceration** as already described.

Diagnostic Criteria

These anatomic features are listed in the table "Scoring System for Diagnosis of Crohn's Disease," and a working definition of Crohn's disease could be the presence of epithelioid granulomas with one other feature, or the presence of three features in the absence of granulomas, provided that specific infection, ischemia, and other recognized causes of tissue damage have been excluded.

The table shows that all the macroscopic features can be recognized by clinical examination, endoscopy, or x-ray. It is thus possible to make a clinical diagnosis on anatomical grounds without microscopic evidence. However, in most cases biopsy adds greatly to the diagnostic information and the usefulness of biopsy has increased now that specimens can readily be obtained under direct vision from the mouth to the duodenum, and from the anal canal to the distal ileum. The reason why diagnosis is so often based on examination of an operation specimen is apparent; all the anatomical features can be looked for.

TABLE

*Scoring System for Diagnosis of Crohn's Disease**

	Clinical	X-ray	Biopsy	Specimen
Ileum	+	+		+
Anus	+	+		+
Fistula	+	+		+
Discontinuity	+	+	+	+
Fissure		+		+
Granuloma			⊕	⊕
Lymphoid			+	+
Mucin			+	+
Transmural				+

* Crohn's = +++ or + ⊕

Limitation of Present Criteria

Diagnostic schemes of this type limit our concept of Crohn's disease to those patients with major structural lesions. It is possible that by so doing, patients with minor inflammation or transient lesions are never recognized, so that Crohn's disease is inevitably regarded as a serious and often chronic or recurring disorder. The newer techniques of endoscopy with biopsy and double-contrast radiology enable small aphthoid ulcers and other minor mucosal abnormalities to be studied. These techniques may enable us to recognize Crohn's disease at an earlier stage than hitherto, when reversion to normal of the structural changes is a possibility. Efforts must be made to define Crohn's disease in terms of minor abnormalities of structure rather than the major abnormalities which are used at present.

Numerical Scoring System: Ulcerative Colitis vs. Crohn's Disease

The Research Committee of the World Organization for Gastroenterology (OMGE) has recently collected detailed data on 1056 patients with inflammatory bowel disease in 30 hospitals in 16 countries (10). To discover how gastroenterologists throughout the world distinguish between ulcerative colitis and Crohn's disease, the data have been analyzed by computer and correlated with the diagnosis of the contributing center to obtain a scoring system, based on likelihood ratios, which can be applied to any patient. Using such a system the overall accuracy of match between the scoring system and clinical diagnosis was 93% (Fig. 2).

The scoring system was then applied to a new set of 510 patients collected from 8 different centers during a different time period; in this analysis the correlation between the diagnostic score and the clinical diagnosis was 96% (Fig. 3).

This technique has defined in numerical terms what experienced clinicians call "ulcerative colitis" and "Crohn's disease" and enables any other doctor to compare his diagnosis with a broadly based consensus view. This system may thus have use in research and as a reference point.

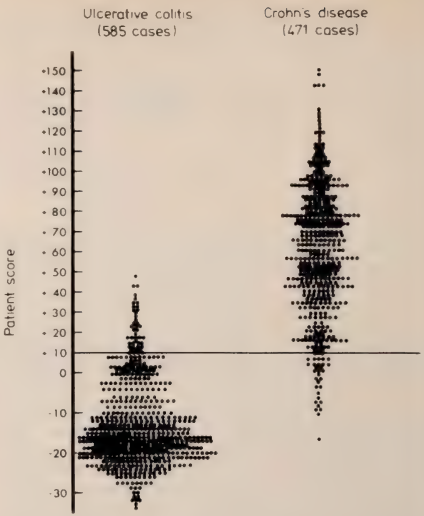

Fig. 2. Retrospective numerical scoring system applied to 1056 patients at 30 hospitals in 16 countries; data collected by Research Committee of World Organization for Gastroenterology. From Clamp et al (10).

Does the Ratio Vary in Different Countries?

The method of data collection and analysis in the OMGE study assured a consensus view of diagnostic criteria used in the distinction between ulcerative colitis and Crohn's disease. It then became possible to apply the common scoring system to patients seen in different centers and find the ratio of ulcerative colitis to Crohn's colitis at each hospital. From the data shown in Fig. 4 it is apparent that there are widely differing ratios between the two forms of colitis at different hospitals in different countries (11). These differences deserve further epidemiological research in future years.

Are the Two Diseases Really so Different?

Clinicians and pathologists may label diseases, but are these names meaningful? Despite their apparent differences, ulcerative colitis and Crohn's disease have much in common. Many studies have shown that about one in ten patients with Crohn's disease has a first-degree relative who also suffers from inflammatory bowel disease. The prevalence of Crohn's disease was 13 times greater than expected among first-degree relatives in a series from Cardiff with almost total ascertainment, a finding most

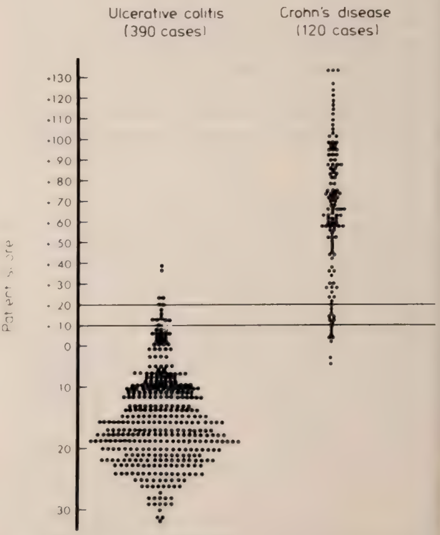

Fig. 3. Prospective application of the scoring system to a new series of 510 patients treated over a different time period at 8 hospitals. From Clamp et al (10).

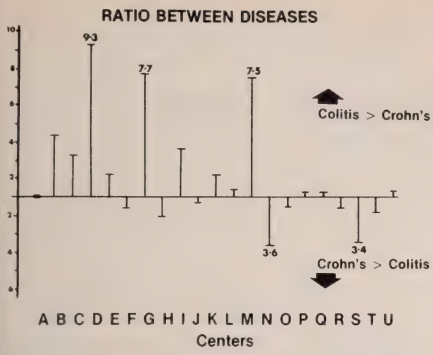

FIG. 4. Ratio between numbers of patients with ulcerative colitis and Crohn's colitis in 20 hospitals in Europe and North America. From de Dombal et al (11).

unlikely ($P < 0.0002$) to have occurred by chance (12). This prevalence is not high enough to indicate a disease of simple Mendelian inheritance with high penetrance.

The results of this survey from Cardiff agree with all other reports that ulcerative colitis also occurs with unexpectedly high frequency in the same families. Another careful study from Liverpool in which all relatives were examined has confirmed that the two disorders tend to occur in the same families, and also ankylosing spondylitis without apparent bowel disease (13). No genetic marker associated with inflammatory bowel disease has yet been recognized. However, those patients with ulcerative colitis or Crohn's disease who are of tissue type HLA-B27 appear to have a greater risk of developing ankylosing spondylitis than subjects of this tissue type in the general population.

These studies suggest that ulcerative colitis and Crohn's disease have a common genetic background. The familial tendency among patients with Crohn's disease tends to be stronger than among patients with ulcerative colitis. Among the families, siblings appear to have a greater risk of developing inflammatory bowel disease than parents, or perhaps children. There is suggestive evidence that a family history of inflammatory bowel disease is particularly common among those who develop one of these conditions in the first two decades of life, a feature suggestive of polygenic inheritance. Several pairs of monozygous twins have been reported, most of whom developed the same type of bowel disease. McConnell (13) has suggested that all these facts may be explained if several genes contribute to a susceptibility to inflammatory bowel disease. If many of these genes are inherited then Crohn's disease is more likely than ulcerative colitis, so explaining the greater familial tendency in Crohn's disease.

Two models appear possible (Fig. 5) to explain the differences observed. First, a single etiological agent may be interacting with subjects of different genetic susceptibility. About half the patients develop a relatively homogeneous disorder (C), which we term ulcerative colitis. Other patients develop a variety of disorders affecting various parts of the gut (A). In the boundary zone (B) we find difficulties in diagnosis and describe the disease as "indeterminate" or "unclassified." Second, there may be two or more etiological agents interacting with susceptible subjects. One agent leads to ulcerative colitis (C). The other agent produces many different varieties of inflammation (A), including colitis in some patients. Where the two manifestations overlap (B) we find classification difficult. Environmental factor(s) and genetic susceptibility, perhaps determined by immunological mechanisms, offer the keys to future advance.

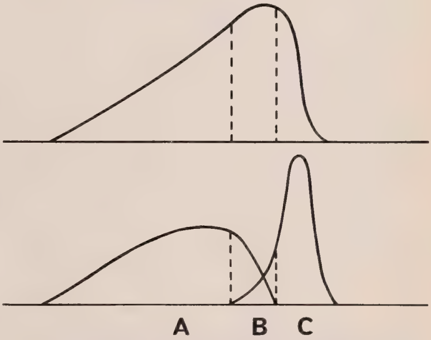

FIG. 5. Two models which may explain the different manifestations of inflammatory bowel disease in patients with a common genetic susceptibility. **Upper diagram:** a single etiological agent interacts with people of different genetic susceptibility. The curve shows the frequency of different clinical manifestations. *A* represents Crohn's disease. *C* represents ulcerative colitis. In the border zone, *B*, classification is difficult. **Lower diagram:** two etiological agents interact with people of similar genetic susceptibility. Agent *C* leads to ulcerative colitis. Agent *A* leads to Crohn's disease. Where they overlap (*B*), diagnostic confusion occurs.

Summary

Crohn and his colleagues little knew that their relatively simple paper was a spark which would cause an explosion of worldwide interest and research over fifty years. It is timely that we salute their memory and press with eagerness into new investigation of an illness which has become increasingly common in many countries during the last fifty years and may perhaps become more widespread in its distribution during years to come.

Acknowledgements

Figures 1, 2, and 3 reprinted from the *British Medical Journal* with the permission of the authors, the editor Stephen Lock, MA, MB, FRCP, and the *Journal*.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Small Bowel Malfunction and Malnutrition

CHARLES D. GERSON, M.D.

Malnutrition in Crohn's disease is quite common and is multifactorial in origin; it is also increasingly important to recognize in view of the nutritional therapy now available. As is often the case, therapy has outraced understanding, and many questions remain concerning the cause, effect, and measurement of malnutrition as well as the effect of treatment. However, it is possible to construct an outline of this problem describing what is known and what is not. This outline includes etiology, nutrient deficiencies, evaluation, consequences, and treatment of malnutrition.

Etiology

Etiology includes oral deprivation, malabsorption, catabolism, and protein leak from the gut.

Oral Deprivation

Anorexia. In Crohn's disease, as in many chronic inflammatory conditions, anorexia appears to be common. Nausea may occur during periods of active disease and eating may aggravate abdominal distress, especially in patients with narrowed ileum. Unknown systemic factors may also play a role. Yet there is little objective data. In several studies of growth-retarded children with ileitis, caloric intake was depressed at 82% of normal in one (1) and 43%–67% of normal in the other (2). Interestingly, protein intake was normal at 107%–177% in the second report. In an unpublished study of fifty adults admitted to The Mount Sinai Hospital with Crohn's disease (3), we made a similar observation: mean caloric ingestion was 1400 calories or 66.3% of normal, while mean protein intake was normal at 95.4 grams. Malnutrition was common in this series. Another group recorded normal or increased intake of calories, protein, and carbohydrates in outpatients with Crohn's disease, but these patients did not appear to be malnourished (4).

Dietary Restriction. Oral deprivation may also result from dietary restriction. This is either self-imposed or advised by physicians, though there is no objective data on the effect of various diets on Crohn's disease activity or symptoms. We recorded dietary intake of ascorbic acid in a group of patients with ileitis and found it to be reduced below the minimal daily requirement in 16 of 36 subjects (Figure 1) (5). This was caused by marked reduction in eating fruits and vegetables. The same phenomenon probably accounts for reduced folate intake (6). Reduced intake of vitamin D in British patients after ileal resection for Crohn's disease has also been carefully documented (7). Although decreased ingestion of iron and magnesium has been suggested, there is no firm data on these nutrients. Despite low serum zinc levels, dietary zinc was normal in 8 of 10 subjects reported on (8).

Malabsorption of Nutrients

Malabsorption of nutrients may be related to six possible factors: ileal inflammation, surgical resection, bacterial overgrowth, jejunal dysfunction, lymphatic blockage, and salicylazosulfapyridine (Azulfidine).

Ileal Inflammation and Resection. A number of groups, including ourselves, have studied the relationship of ileal disease and ileal resection to malabsorption of fat, vitamin B_{12}, and bile salts (9–13). Several points deserve emphasis. In patients with ileitis who have not had resection, bile salt and fat absorption is usually normal and there is poor correlation between length of disease and Schilling test results. After resection, correlations are signifi-

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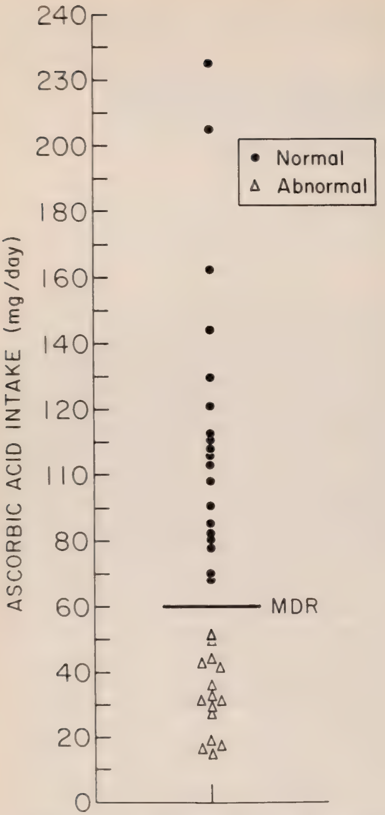

FIG. 1. Ascorbic acid intake in patients with Crohn's disease.

cant for all three nutritional elements and the critical length for impaired absorption is around 30 cm for bile salts, 60 cm for B_{12} and 90 cm for fat. The patients with bile salt loss but without steatorrhea are the ones who suffer from cholerrheic diarrhea and often respond dramatically to cholestyramine. Since steatorrhea is the most nutritionally relevant consequence, a large resection must occur before malabsorption of clinical importance ensues. Malabsorption is critical only in patients with a short-bowel syndrome.

Bacterial Overgrowth. Patients with a short segment of disease and abnormal Schilling test results may have bacterial overgrowth due to stricture or fistula. While there is some evidence for increased jejunal bacteria in Crohn's disease (14), ileal flora and their contribution to malabsorption are not known.

Jejunal Dysfunction. It has been suggested that the entire gut is involved in Crohn's disease even when gross duodenitis and jejunitis is not present. Jejunal function has been studied and it is not yet clear whether it is normal or abnormal. We have measured jejunal absorption of water, sodium, chloride, glucose, and folic acid using an intestinal perfusion technique over a 30-cm segment and the results were normal (15). Jejunal salt and water transport was also normal in one other perfusion study (16). A group using a radioisotope method found decreased bidirectional sodium flux along the entire small intestine (17). Abnormal jejunal mucosal structure and enzyme activity has been reported (18). We measured D-xylose excretion in the urine, a measure of proximal intestinal function, in a large series of patients with Crohn's disease, excluding those with jejunitis or short-bowel syndrome (9). Although most subjects had excretion above five grams in five hours, the results were also assessed by drawing a distribution curve, a method that displays results for a study population (Figure 2). This showed that the curve was shifted to the right when compared to a normal curve (19) and suggests that xylose absorption for this population may be depressed. More specific measure of function of the jejunum is required to resolve this problem.

Lymphatic Blockage. In reference to folic acid, malabsorption may occur in Crohn's disease, but this is due to the inhibitory effect of salicylazosulfapyridine (Azulfidine) on folate absorption (15, 20). This has been well charac-

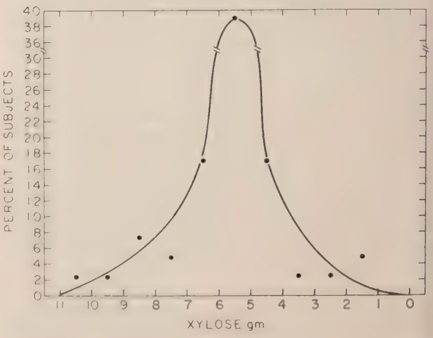

FIG. 2. Xylose excretion distribution curve related to percent of study population, regional enteritis.

terized and does contribute to folate deficiency. The quantitative consequences of lymphatic blockage on fat absorption and protein leakage are not known.

Catabolism

Inflammation and Corticosteroids. The catabolic effect of chronic inflammation undoubtedly contributes to malnutrition. Metabolic alteration also is caused by corticosteroid therapy. The only evidence for the catabolic effect of disease are the apparent increased caloric and protein requirements of adult and adolescent malnourished patients with Crohn's disease for weight gain and positive nitrogen balance. The requirements have been estimated at greater than 80 calories per kg in adolescents (21) and greater than 50 calories per kg in adults (22).

Protein Leak

Protein leak from the gut compounds this problem. While the metabolic effects of inflammation are difficult to quantify, protein loss into the gut can be measured, correlates significantly with length of mucosal inflammation, and clearly has an adverse effect on nitrogen balance (23).

Of all the above factors, decreased intake, increased energy utilization, and protein leak are probably the most important causes of malnutrition. Certainly many patients are malnourished who have no sign of malabsorption, including those with granulomatous colitis alone. It is to be hoped that this problem will be better documented in the future.

Nutrient Deficiencies

Clinical manifestations of inadequate nutrition include vitamin and mineral deficiency and protein-calorie malnutrition. Vitamin deficiency affects both water-soluble and fat-soluble vitamins. We have measured ascorbic acid levels in serum and white cells in patients with ileitis and found results below the normal range in 50% (5). Folic acid deficiency has been reported in over 50% of patients, probably due to reduced intake and Azulfidine induced malabsorption (6–20). Other B vitamins have not been well studied. Despite abnormal Schilling test results, it is unusual to see megaloblastic anemia and low serum B_{12} concentration. Fat-soluble vitamins may be lacking in patients with large resections and large bile salt losses. This has been found in a study of 25-OH vitamin D, in which low intake and poor absorption contributed to low serum levels (7).

Inadequate mineral stores have been suggested in studies of serum zinc (24) and iron levels (25) and magnesium deficiency has also been described (2). The etiology has not been clearly delineated, although a combination of factors is probably responsible. While serum 25-OH vitamin D concentration may be low, serum calcium deficiency is relatively uncommon, especially when low albumin is accounted for. Even with normal serum calcium, bone biopsies may show evidence of osteomalacia (27).

Consequences

The main consequence of inadequate nutrient supply is protein-calorie malnutrition (PCM). PCM can be precisely diagnosed only where research units can quantify body compartments such as total body nitrogen with special isotope techniques. In lieu of this, a number of measures have been used, including anthropometric tests, serum protein levels, skin testing, and creatinine/height ratios. Results with such measures suggest that the best estimate of PCM comes from a careful history and physical exam, loss of more than 10% of the pre-illness weight, and inability to maintain normal nutrient intake (28). Anthropometric tests such as triceps skin fold (TSF) for body fat stores, arm-muscle circumference (AMC) for lean body mass, and weight/height may be reliable for a large study population but not for the individual patient because of a large range of error (29, 30). Also, it has been arbitrarily suggested that values 10% below normal be considered abnormal without statistical validation (31). The variation in data distribution curves for different measures invalidates such a standard. Serum protein levels for visceral protein assessment include albumin, transferrin, thyroxine-binding prealbumin (TBPA), and retinol-binding protein (RBP). Half-lives are respectively nineteen days, eight days, two days, and twelve hours. This makes TBPA and RBP the appropriate proteins to follow if change in visceral protein is being monitored during hospitalization (32). Serum albumin is not highly accurate as a measure of PCM since it is affected by many factors. However, low albumin may be useful as a prognostic indicator (33, 34). The same holds true for transferrin unless iron deficiency is present since it may raise blood transferrin levels. Skin testing for delayed hypersensitivity has also been validated as an indicator of poor prognosis if anergy is found (33, 34). PCM can have a profound effect on immunocompetency (35). Antigens should include mumps, candida, and streptokinase/streptodornase; some groups also use purified protein derivative and trichophyton. As an indicator of PCM, lymphocyte depletion is not as reliable as anergy. Creatinine/height ratio also has not been found to be an accurate marker of PCM or prognosis.

Of all these measures, serum albumin and skin testing for anergy generally have proved the most useful prognostic markers. Skin testing is not that useful in Crohn's disease, since anergy may be found in association with ileitis or steroid therapy regardless of the nutritional status of the patient (36).

In Crohn's disease, low serum albumin is a common finding. We found serum albumin below 3.5 gm/dl in 35 of 53 hospitalized patients with Crohn's disease in a previous study (9) and in a group we recently evaluated, albumin was depressed in 36 of 44 patients (3). Twenty-four of those subjects had albumin below 2.8 gm/dl (Figure 3). Weight loss is also well documented and was 10% or greater in 22 of 44 subjects in our study (Figure 4). There is very little data available on other measures of PCM in Crohn's disease, except for data on severely malnourished patients in long-term nutritional repletion studies.

In addition to albumin and weight loss, we recently measured serum transferrin, triceps skin fold (TSF), arm-muscle circumference, weight/height and peripheral lymphocytes in our subjects. Transferrin concentrations tended to resemble the albumin data, with low serum levels in 29 of 48 patients (Figure 3). Results for AMC were also abnormal in a majority of subjects. TSF tended to be distributed more normally. When compared to data obtained from the Ten States Nutrition Study (37), 45 of 48 patients had AMC below the fiftieth percentile of a normal population, whereas only 29 patients had TSF below that percentile (Figure 5). Values were below the fifth percentile for AMC in 22 and for TSF in 6 subjects. This suggests that lean body mass was more severely affected than fat stores. Weight for height was below 90% of normal in 23 of 46 subjects, paralleling the findings for weight loss (Figure 4). Correlations were significant between triceps skin fold and weight for height, and between arm-muscle circumference and both weight loss and weight for height.

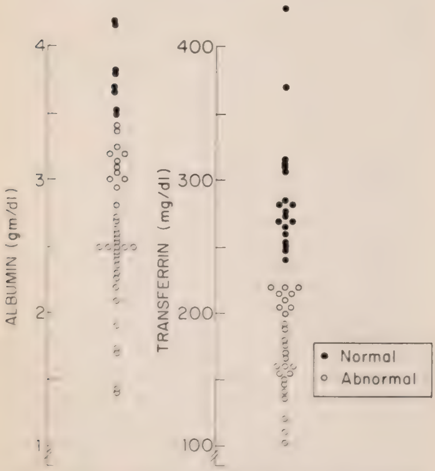

FIG. 3. Serum albumin and serum transferrin in hospitalized patients with Crohn's disease.

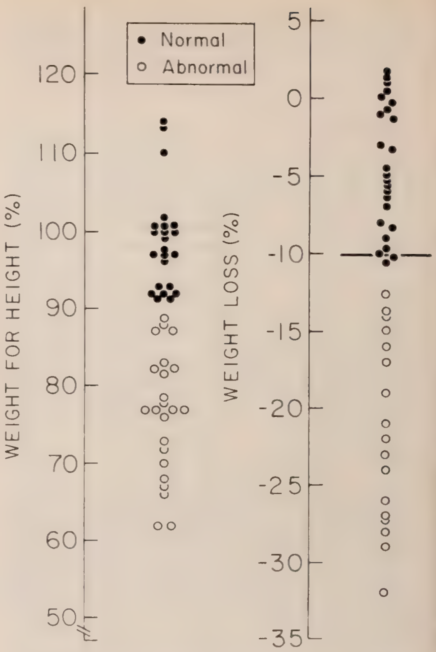

FIG. 4. Percent weight loss and weight for height.

Lymphocytes were low in half our patients,

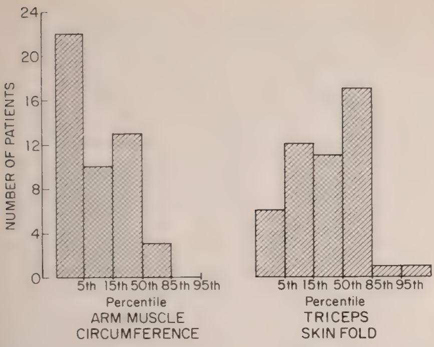

FIG. 5. Comparison of arm-muscle circumference and triceps skin fold in Crohn's disease population and normal population in Ten States Nutrition Study.

but Crohn's disease appears to be associated with lymphopenia and anergy regardless of clinical status (36).

While PCM has a deleterious effect on immunocompetency, which should be common in the visceral protein deficiency seen in Crohn's disease, many questions remain concerning its effect on the disease course. Growth retardation has been strongly associated with malnutrition (1, 2). Poor caloric intake and other parameters of PCM are associated with a reduction in height curves to the right, usually with normal weight for height. This results in a form of nutritional dwarfism. In adults with Crohn's disease, effects of PCM on inflammation, fistula formation, response to medical treatment, and surgical complications are not clear. We found that patients with fistulae had an associated ascorbic acid deficiency (5) but there have been no other similar nutritional studies. We also recently examined the relationship between serum albumin on admission to hospital and length of stay in hospital. We found that patients with depressed albumin below 2.5 g/dl tended to have long hospital stays (Figure 6). Seven of nine patients with albumin greater than 3.0 g/dl on admission were in hospital less than two weeks, whereas 13 of 16 patients with albumin less than 2.5 g/dl had hospital stays of more than two weeks. This suggests that malnourished patients have more disease activity or may be more resistant to medical treatment. Although PCM may be a result rather than a cause of more disease activity, this observation may help to point to the patient who will benefit from nutritional therapy.

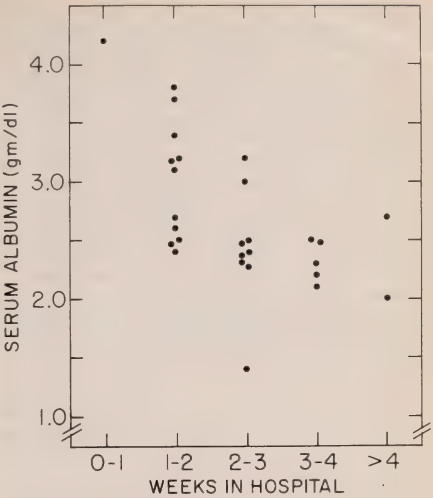

FIG. 6. Relationship between serum albumin on admission and length of stay in hospital.

Treatment

Treatment of malnutrition may take a number of forms. Total parenteral nutrition (TPN) has been the most publicized, but enteral feeding via nasogastric tube, oral supplements, vitamins and minerals, and home hyperalimentation are also available and all may be utilized in Crohn's disease. The two problems that most clearly require nutritional therapy are growth retardation in adolescents and severe malabsorption in patients with either short-bowel syndrome or diffuse inflammation involving the entire small intestine. In adolescents, caloric and nutrient supplementation brings growth curves back toward the pre-illness percentile through augmented growth spurts (1, 2). Sometimes medical therapy has a complementary effect.

Controversial indications for TPN have been the presence of fistulae, desire to avoid surgery, and preparation for surgery. Most reports of long-term follow-up have been unable to show sustained closure of fistulae after TPN. Earlier enthusiasm may have been engendered by the response of fistulae in patients who did not have inflammatory bowel disease. While control trials of nutritional therapy in Crohn's disease have not been reported, ileitis activity may respond to TPN or enteral hyperalimentation and this can allow sick patients to avoid surgery temporarily or even for a sustained period (22, 38). It is well known that putting the bowel to rest is beneficial in Crohn's disease. In addition, improving nutritional status may have its own benefit. Weight gain and positive nitrogen balance have been documented in these patients. While long-term remission has been observed, most will relapse eventually. In patients who are definitely earmarked for surgery, preoperative nutritional supplementation would appear to be advisable if PCM is present. Although there is no controlled data on the effect of such treatment in Crohn's disease, there is evidence from other surgical reports, for example, in gastrointestinal cancer, of fewer complications in patients who had PCM and were nutritionally repleted (39). Patients with strictures and partial obstruction from ileitis usually require parenteral therapy, but many subjects without obstructive symptoms can tolerate enteral hyperalimentation with elemental diets. Efforts to increase oral intake may suffice, obviating the need for a nasogastric feeding tube. Oral supplements can include elemental formulas and polymeric defined formulas. A low-fat diet supplemented with medium-chain triglycerides may be effective in patients with significant malabsorption with steatorrhea.

Despite these recommendations, there is a need for controlled trials with nutritional supplementation in patients with PCM and Crohn's disease. Until such trials are conducted, decisions regarding therapy will be largely based on individual physician bias and experience. This may result in some patients being unnecessarily treated and others being denied the nutrients that could improve their clinical course.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Extraintestinal Manifestations

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The systemic manifestations of inflammatory bowel disease (IBD) are quite common. In most patients, the complications are not disabling and usually respond to the underlying management of the disease. On rare occasions extraintestinal manifestations can be severe and create more debility than the IBD itself, as for example blindness in an eye, in a patient with complicating uveitis. IBD can produce traumatic emotional responses in children with severe growth retardation, and in extreme circumstances can result in death (amyloidosis and cirrhosis).

Table I offers an overview of extraintestinal manifestations of IBD. The most common sites of involvement are joints, skin, eye, liver, and kidney. However, every year new complications are reported in the literature on these diseases. In 1982 there were reports of pulmonary involvement, pericarditis, and pseudothrombophlebitis. Each of these reports awaits confirmation: is the manifestation truly an extraintestinal complication, or is it a fortuitous combination of two diseases? Since this is a Mount Sinai symposium, I think it is appropriate to look at the first fifty years of Crohn's disease and the role of this institution in the learning process in regard to extraintestinal manifestations.

Table II shows contributions made by Mount Sinai physicians. To keep the list concise, I tried to avoid repeating names because many authors appeared multiple times. The classic monograph by Crohn and Yarnis (1) was the precursor of what is now the classic paper on extraintestinal manifestations, by Greenstein, Janowitz, and Sachar (2). Twenty years ago Deren, Levitt, and Khilnani (3) pointed out the major impact of urolithiasis in IBD and also described beautifully some of the mechanisms of stone formation. Drs. Ginzburg and Oppenheimer (4), back in 1948, published some of the early findings on urological complications. This was followed by a publication by Drs. Goldman and Glickman (5), who are still practicing urologists at this hospital. I had the pleasure of working with Dr. Rabinowitz, who is our current chairman of the Department of Radiology, and Dr. Banks (6) on a paper describing the manifestations of hydronephrosis with the first description of left ureteral obstruction in Crohn's colitis. Drs. Gerson and Cohen (7) have given us some widely quoted classic papers on absorption. We then come to another classic paper on uveitis, by Drs. Korelitz and Coles in 1967 (8). Our pediatrician, Dr. Gribetz (9), made some major contributions with papers on growth. Dr. Alan Silverstein (10) published a paper on neurological complications in young patients, and I hope in the near future Dr. Gendelman will be publishing the largest collected series on neurological complications of IBD.

Recent papers are not usually listed as classics, but our younger generation is following in the same tradition at Mount Sinai and there have been recent papers by Drs. Altman (11), Meyers, and Mayer (12) on cutaneous gangrene and cryoglobulins, one by Dr. Fabry (13) on myelogenous leukemia in association with IBD, and most recently, Drs. Finkel (14) and Talansky (15) have added to the current literature. The interest in IBD is unflagging at Mount Sinai Medical Center

Immune Complexes as Mechanism

Before covering the clinical highlights, I would be remiss not to mention current concepts of mechanism in pathogenesis. The immunologic approach has been foremost in most recent research laboratories. Although I am not an immunologist, in reviewing the literature it appears that circulating immune complexes have been highest on the causative list of mechanisms. Circulating immune complexes have been demonstrated in both Crohn's and ulcerative colitis, but the reports of concentration and frequency of these complexes have

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TABLE I
*Extraintestinal Manifestations of IBD**

Site	Percentage in All IBD Patients
Joints	23
Skin	15
Eye	4
Liver	3
Multiple	30

* Adapted from Greenstein, Janowitz, and Sachar (2).

really been conflicting. Hodgson (16) and Fiasse (17) felt that the presence of immune complexes seemed to correlate with the presence of extraintestinal manifestations and disease activity. Other reports in the literature have demonstrated a decrease in immune complexes if the patient underwent surgical removal of Crohn's disease or responded to therapy with steroids. Unfortunately, most of the studies cannot correlate levels of immune-complex changes with disease status in specific patients. Lawley (18) has found that the complement system is in an activated state in these diseases, and that the alternate complement pathway is activated as well. This latter alternate pathway is most marked in patients with extraintestinal manifestations. Since circulating immune complexes are seen more frequently in those patients with colonic disease, it has been speculated that this may be due to the higher concentration of bacterial antigens in the colon as compared to the small bowel, which could then be providing the sensitizing antigens. In an interesting paper, Kemler and Alpert (19) have found circulating immune complexes which were specifically related to IBD and were not found in patients with other colonic inflammatory diseases such as pseudomembranous and bacterial colitis. They suggest that the mere disruption of the mucosal barrier was not a nonspecific finding resulting in circulating immune complexes. However, as I review the literature, in almost all immunological studies, the authors often question the "pathogenetic" significance of these complexes. Lastly, hypogammaglobulinemia has been documented, which implies that immunoglobulins may be sequestered in these immune complexes. Much remains to be done by immunologists in this aspect of IBD.

Clinical Data

It is impossible to cover the clinical data on even one extraintestinal manifestation in a short discussion; I therefore try to quickly cover the highlights. Here, extraintestinal manifestations in Crohn's disease are contrasted with ulcerative colitis, since this is the way it is usually reported in the literature.

The overall frequency of extraintestinal manifestations is approximately 35%. The manifestations seem to be the same in Crohn's disease and ulcerative colitis, with some notable exceptions: aphthous ulceration and erythema nodosum, seen more commonly in Crohn's disease, and pyoderma gangrenosum, more common in ulcerative colitis. The most common complications—joints, skin, mouth, and eye—appear to be associated with colonic involvement.

In terms of organ involvement (Table I), the musculoskeletal system is most often affected (23%), followed by the skin (15%), the eye (4%), and the liver (3%). Tables III and IV come from Dr. Greenstein's experience with patients at Mount Sinai (2). The authors divided 700 pa-

TABLE II
Extraintestinal Manifestations of IBD
Mount Sinai Contributions

1. Retrospective Reviews	Crohn, Yarnis	(1958)
	Greenstein, Janowitz, Sachar	(1976)
2. Amyloidosis	Werther	(1960)
3. Urolithiasis	Deren, Levitt, Khilnani	(1962)
4. Urological complications	Ginzburg, Oppenheimer	(1948)
	Present, Rabinowitz, Banks	(1969)
	Goldman, Glickman	(1973)
5. Absorption	Gerson, Cohen	(1973)
6. Uveitis	Korelitz, Coles	(1967)
7. Growth	Gribetz	(1962)
8. Neurological	Silverstein	(1971)
9. Cutaneous gangrene	Altman, Meyers	(1979)
10. Myelogenous leukemia	Fabry	(1980)
11. Pyoderma gangrenosum	Finkel	(1981)
	Talansky	(1983)

tients with IBD showing extraintestinal manifestations into two populations. Patients with manifestations related to colitis (Group A) showed involvement of the joint, skin, mouth, and eye (Table III). This was observed most commonly in Crohn's colitis, as compared to the Crohn's ileitis group. Group B had manifestations which the authors related to abnormal pathophysiology of the small bowel, including malabsorption, gallstones, renal stones, and noncalculus hydronephrosis (Table IV).

Joint Manifestations

Of the individual manifestations, joint disease is considered to be the most common. It was originally thought to be more frequent in ulcerative colitis, but an equal incidence is likely in both Crohn's disease and ulcerative colitis. At Mount Sinai, joint involvement occurred in 23% of patients (2). The literature records ranges from 4% to 22%. Arthritis in Crohn's disease is highest in colitic patients, intermediate in ileocolitis, and lowest in ileitis. There are essentially four types of joint involvement.

The monoarthritis pattern is the most common variant. The onset may be acute or subacute. It is self-limited in most patients, usually lasting up to two months. However, about 10% of patients may go on to have continuous arthritic complaints for up to one year. There may be hot, warm, tender joints, frequent effusions, elevated sedimentation rates and white blood cell counts and negative tests for rheumatoid factor. As the years pass, this type of arthritis seems to decrease in Crohn's disease, being most prevalent in the first five years. The activity in the joints parallels the activity of the bowel disease. Occasionally the arthritis can precede the bowel disease, especially in children. In the polyarthritic group, the onset seems to be less severely acute and somewhat more subacute. The duration is shorter, perhaps lasting up to a few weeks, and again most commonly affects the large joints of the lower extremities. Both these diseases respond to aspirin and nonsteroid antiinflammatory drugs and rarely are a major clinical problem in management. Sacroileitis is mostly asymptomatic or occasions minimal discomfort and is detected on routine barium studies and other x-rays of the abdomen. Sacroileitis is not related to HLA-B27 typing.

Ankylosing spondylitis is seen in 4% of all IBD patients, as compared to less than 0.1% in the normal population. There is also a 2-to-1 male-to-female ratio in IBD, as contrasted to 9 to 1 in the non-IBD population with ankylosing spondylitis. Of IBD patients with ankylosing spondylitis, 75% to 90% are HLA-B27 positive, whereas the Crohn's patients with peripheral arthritis and IBD are HLA-B27 negative. If you have Crohn's disease and you are B27 positive, the risk of developing ankylosing spondylitis is 16%. If you have ulcerative colitis and are B27 positive, the risk is 47%. The usual symptoms are back pain, stiffness, and limitation of motion; the process can also affect some of the larger joints such as the hips, shoulders, and knees. However, compared to peripheral arthritis, in which the activity of the joints is synchronous with the activity of the bowel, spondylitis can occur long before the onset of overt clinical disease, and the course of the spondylitis is not related to the severity, the chronicity, or the activity of the bowel disease. Medical therapy including surgical resection does not necessarily affect the progression of the spondylitis. We treat this manifestation with analgesics, Indocin, nonsteroid antiinflammatory drugs, and physiotherapy, with varying success.

Skin Manifestations

A long list of skin lesions may be noted which occur in 15% of patients. Once again,

TABLE III

*Group A: Colitis-Related Extraintestinal Manifestations**

(700 Patients with IBD)

Type	Ulcerative Colitis (202)	Granulomatous Colitis (62)	GI Colitis (223)	Regional Enteritis (213)
Joint	53(26%)	24(39%)	57(26%)	30(14%)
Skin	39(19%)	14(23%)	36(16%)	19(9%)
Mouth	8(4%)	7(11%)	7(3%)	6(3%)
Eye	9(4%)	8(13%)	10(4%)	2(1%)
TOTAL	90(45%)	32(55%)	83(37%)	50(23%)

* Adapted from Greenstein, Janowitz, and Sachar (2).

TABLE IV

*Group B: Extraintestinal Manifestations Related to Small-Bowel Pathophysiology**
(700 Patients with IBD)

Type	Ulcerative Colitis (202)	Granulomatous Colitis (62)	GI Colitis (223)	Regional Enteritis (213)
Malabsorption	1(.5%)	0(0%)	22(10%)	23(11%)
Gallstones	10(5%)	3(5%)	22(10%)	27(13%)
Renal Stones	11(5%)	3(5%)	21(9%)	18(8%)
Hydronephrosis	0(0%)	2(3%)	14(6%)	12(6%)

*Adapted from Greenstein, Janowitz, and Sachar (2).

skin complications are seen most commonly in colitis and less so in ileitis. Erythema nodosum is the most frequent skin manifestation (in about 15% of Crohn's colitis). The nodosum seems to be more frequent in women and children, is synchronous, and parallels the course of the disease activity. It usually affects the anterior aspect of the lower extremities with evidence of moderate tenderness. It is very often associated with arthritis and fever.

Pyoderma gangrenosum at Mount Sinai as well as at other institutions appears to be more common in ulcerative colitis—5%, as contrasted with 1.4% of the Crohn's group. The lesion usually occurs on the tibia, near the medial malleolus, but can be seen in other areas of the body. Initially you have pustules which coalesce, break down, and form large gangrenous ulcers, which characteristically are ragged, irregular, with overhanging edges and necrotic bases. Pyoderma gangrenosum has been described without inflammatory bowel disease. Pyoderma also does not necessarily follow the activity of the IBD. It can occur before the onset of the bowel disease. As noted above, Dr. Finkel (14), at this institution, has recently published a paper reiterating the role of trauma in preceding pyoderma in five cases. Four had no increase in colitis symptoms at the time of the development of the pyoderma. The pyoderma often responds to local therapy, steroids, sulfasalazine, and/or antibiotics, but pyoderma may persist despite surgical extirpation of the diseased bowel.

Eye Manifestations

There is a wide range of ocular complications ranging from episcleritis, to conjunctivitis, to orbital cellulitis. The one that is most feared is uveitis. Uveitis is seen in about 4% in the Mount Sinai series, which is somewhat less than the rest of the literature. Once again, it occures most frequently in Crohn's colitis, least in ileitis. There is a slightly increased female-to-male ratio. Involvement is usually in the anterior uveal tract, and appears to be immunological in origin, whereas posterior uveitis is usually seen with secondary infections and bacterial invasion. Symptoms consist of pain around the eye, which is markedly reddened, more so than in conjunctivitis. With a slit lamp, you can see keratotic precipitates in the cornea. The classic paper by Korelitz and Coles (8), from this institution described thirteen patients with uveitis, two of whom went on to visual deficits. One became totally blind and one had severe vision loss. Korelitz and Coles noted the lack of correlation between the appearance of the uveitis and the gut activity, suggesting no causal relationship. In four of the thirteen, the uveitis preceded the onset of the IBD. Episcleritis is a milder form of inflammation of the sclera, and is usually located in the temporal aspect of the eye. The ocular complications usually respond to topical steroids if the bowel is quiet; if the bowel is active, a combination of topical and systemic steroids may be required.

Mouth Manifestations

Since oral manifestations were brought up in prior discussion, I note some classic papers by Basu and Asquith (20), very interesting to read, describing oral complications in 6% to 20% of patients. These complications are seen in both Crohn's disease and ulcerative colitis and appear to be higher in colonic disease. Mouth lesions are also associated with other extraintestinal manifestations, such as skin and joint involvement. They may precede the onset of symptomatic intestinal disease, but in most cases occur at the time of active disease. The process can be chronic or periodic, and can be either very painful or asymptomatic. The lesions range from simple aphthous ulcerations to fissuring, to what is described as cobblestoning in the mouth, with polypoid tags, and linear ulcerations. Biopsies in 10% showed noncaseating granulomata. Biopsy of uninvolved buccal mucosa in IBD often shows nonspecific inflammation, and there is evidence of abnormal immunofluorescent staining in biopsies from normal lips of IBD patients. Parotid IgA secretion is depressed in Crohn's disease, and not in ulcerative colitis. This IgA depression appears to continue as the gut disease increases. There is evidence of circulating immune complexes in some of these patients with oral lesions.

Gallstones

Other complications include gallstones, which are mentioned in Dr. Greenstein's paper as occurring in about 9% of patients. The incidence is higher in small-bowel than in colonic involvement. In the world literature, the incidence of gallstones appears to be higher (30%–35%). The mechanism is probably the result of disease or resection of the terminal ileum with increased fecal excretion of bile salts in hepatic bile. This reduces the ratio of gallbladder bile salt to cholesterol, decreasing solubility, and thus forming cholesterol precipitation and gallstones.

Liver Manifestations

The spectrum of liver complications is seen in both ulcerative colitis and Crohn's disease, except for bile duct carcinoma, which in the literature occurs mostly in association with ulcerative colitis. At Mount Sinai, significant liver disease was seen in less than 5%, which correlates with the literature. However, if you review the studies in which biopsies are taken in surgical patients, the findings go as high as 50% to 100% (21). These abnormalities may reflect the nutritional status of these very ill patients who are requiring surgery. If biopsies are done with a Menghini needle, abnormalities are seen in about 30% of patients. Pericholangitis, and fatty infiltration of the liver, are the most common findings, and are seen in about 30% to 50% of IBD patients. This usually accounts for the slightly elevated alkaline phosphatase concentration seen in active patients admitted to the hospital. Biopsies show focal acute and chronic portal inflammation. Most patients with liver disease are asymptomatic but a few progress to fibrosis and secondary biliary cirrhosis. One third of all patients with sclerosing cholangitis have IBD, but the reverse is that less than 1% of IBD patients have sclerosing cholangitis. This is associated with jaundice, pruritus, fever, and right upper quadrant pain, and biopsies show pericholangitis often going on to severe hepatic changes. Endoscopic retrograde cholangiopancreatography is probably the best diagnostic procedure. Medically there is little we can do, because most of these patients do not respond well to steroids, or even surgical removal of the bowel. Ultimately the surgeon may have to perform an internal drainage procedure. It can be quite difficult to clinically distinguish sclerosing cholangitis from bile duct carcinomas. Bile duct carcinomas have been reported in about 0.4% to 1.4% of ulcerative colitis patients and are rarely reported in Crohn's disease. I personally have seen two cases in the last two years of bile duct carcinoma associated with Crohn's disease, but they have not been reported. Other liver disease, such as chronic active hepatitis and cirrhosis, are seen, but it must be reiterated that significant clinical disease of the liver occurs in less than 5% of all IBD patients.

Urologic Manifestations

In my practice experience, the urologic complications appear to be the most troublesome. In Dr. Greenstein's series, the incidence of stones was 7.6% and was higher in small-bowel cases than in colonically involved cases. Knudsen's study (22), in which he used only patients who had IVPs in inflammatory bowel disease, showed a stone incidence of 15%. The incidence appeared to increase with small-bowel resection, especially if over 50 cm was removed. The most commonly observed type is the calcium oxalate stone; however, there is also an increased frequency of uric acid calculi as compared to the normal population. The current mechanism theory is felt to be hyperoxaluria. Following an ileal resection, bile acid absorption is decreased, and increased bile acids appear in the colon, enhancing oxalate absorption and subsequent hyperoxaluria. This is not the only mechanism, since ileostomy patients who do not have hyperoxaluria also have increased calculi. Malabsorption also tends to be associated with an increased incidence of stones. Calcium, which usually binds oxalate, combines with fatty acids to form soaps. The lack of calcium makes oxalate more available for absorption. But the oxalate story is not the only factor in these patients. Other factors include dehydration, oliguria, obstruction of ureters, and abnormal uric acid excretion, and many patients often have persistently acid urine. These may result in uric acid calculi; steroids may on occasion lead to hypercalciuria. The management of stones I leave to our urological colleagues, but prevention is important. You must try to maintain your patients in a well-hydrated state as well as correcting the electrolyte abnormalities and the malabsorption. Patients should be maintained on a low oxalate diet, the urine should be alkalinized in those patients who have a persistently low urinary pH, and allopurinol must be used in some patients.

Dr. Ginzburg was one of the first to describe hydronephrosis. Clinically, it is an important entity in that the patients usually have few urinary symptoms (occurring in 30%) and the urinalysis is abnormal in only 10%. These patients often present with fever and flank, hip, or thigh pain. The presentation is usually that of the inflammatory bowel disease. One of the first patients I saw here, in April 1967, with classical ileal involvement and hydronephrosis underwent only an ileostomy, with resection of the disease, and showed significant clinical improvement and alleviation of the hydronephrosis. Likewise, in a patient with colonic disease, most severe in the sigmoid colon, you may have hydronephrosis on the left side, whereas most cases are on the right side. Following ileostomy alone, the patients show decompression of the ureter. There is much written in the literature about ureterolysis, Dr. Block (23) being the major advocate. At Mount Sinai Hospital we do not perform ureterolysis. The surgical treament of the primary bowel disease is adequate to get the majority of patients better. In the extensive fifty-year history of IBD at Mount Sinai, only one kidney has been lost from hydronephrosis. This case of hydronephrosis is one of the initial series that I reported in 1967 (diagnosed on the basis of hip pain). She had the worst hydronephrosis I have ever seen. We treated her medically and initially she really wasn't much improved. She refused surgery and left the hospital. In 1969 she had another set of films that showed some improvement of the hydronephrosis, and finally films in 1970 showed no change in the hydronephrosis. At this time she was having absolutely no symptoms from her IBD. It is interesting to note the natural history of a patient who refused to have surgical intervention and who essentially showed no deterioration over a six-year period. We have seen numerous patients who have been treated medically (with steroids, Azulfidine, or antibiotics) and whose hydronephrosis has improved without surgery.

The next-to-last complication I discuss here is ileovesical fistula, which is described in Dr. Greenstein's series in about 7%. The symptoms are usually related to bowel activity plus the associated passage of air and/or debris in the urine. The fistulae are suspected clinically but are difficult to visualize radiographically. Intravenous pyelogram shows irregularity of the dome of the bladder. Cystoscopy does not add significant clinical information. Most patients quickly come to surgical intervention, but medical management has been sucessful for many patients in our personal experience.

The last complication I want to discuss is amyloidosis (24). The incidence is about 1% to 8%. There are only 28 cases reviewed in the literature up to 1980 (25). Usually these patients had amyloid with proteinuria and nephrotic syndrome. The onset could be anywhere from three to fifteen years after the diagnosis of Crohn's disease and, contrary to what was thought initially, there was no definite relation to fistulous complications. Attempts to treat these patients with steroids and with surgery have met with little success. Of the 28 patients, 14 had surgery. Six died in six months, of renal failure. Four were undergoing dialysis or transplants, three developed recurrent Crohn's disease, and only one patient had regression of the amyloid. So although regression is seen, surgery cannot be advocated easily for these patients, as it often acutely worsens the renal function and patients often die of renal failure.

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The Mount Sinai Journal of Medicine
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

New Concepts of Cancer

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Everybody else has been talking about history this morning, so I would like not to be left out. I would like to point out that there is another anniversary this year pertaining to inflammatory bowel disease. This is the twenty-fifth anniversary of the publication of the first two cases of small bowel cancer in ileitis, reported by Dr. Leon Ginzburg and his colleagues in 1956 and 1957. But what we are supposed to talk about today, according to the title of the program, is *newer* concepts of cancer in inflammatory bowel disease. So I must start off by asking what can possibly be new? We see that it has been twenty-five years since we recognized, thanks to Dr. Ginzburg and his colleagues, the problems of small bowel cancer in ileitis; while in ulcerative colitis the original report of cancer occurring in the colon is well over fifty years old. The classical concepts of cancer in ulcerative colitis and Crohn's disease are therefore all old concepts, so what's new?

Let us look first at some of these classical concepts of cancer in inflammatory bowel disease. In ulcerative colitis, the first classical concept is that there is an increased risk of colorectal cancer. It has long been taught that the risk factors for cancer are greatest for colitis with long duration, universal distribution, and childhood onset. We have also been taught over the years that colorectal cancer, when it occurs in ulcerative colitis, has a worse prognosis than cancer in the general population. With respect to Crohn's disease of the colon, the classical teaching has been that even if there is some increase of cancer risk, it is really nowhere near the magnitude of the problem in ulcerative colitis. We also have learned about cancer occurring in the small bowel in patients with ileitis; the classical concept in these cases is that there is some particularly high risk associated with a bypassed loop. In the last few years, however, from studies here at Mount Sinai and elsewhere, there are new concepts developing that in some cases reinforce, but in other cases modify, classical concepts. Some of these new concepts have developed from the vast clinical experience of our Surgical Department, notably from Dr. Aufses, Dr. Kreel, Dr. Gelernt, Dr. Slater, and many of their colleagues, and particularly from the meticulous statistical reviews and analyses that have been spearheaded by Dr. Greenstein.

Ulcerative Colitis and Colorectal Carcinoma

Looking first at ulcerative colitis, let us examine five of the classical concepts concerning cancer in this disease. The first classical concept has certainly withstood the test of time. It is a clearly increased risk of developing colorectal cancer in ulcerative colitis. The cancer-incidence curve in Figure 1 is derived from data at Mount Sinai (1), but there is nothing new about this information. Over the past twenty years, statistics derived by actuarial (life-table) methods are very similar in different decades and different locations, including the General Infirmary in Leeds (2), The Mayo Clinic (3), and the University of Göteborg (4).

The second classical concept has also held up over the years. The appearance of increased cancer risk takes a long time. Before 8–10 years of disease, it has not been possible to demonstrate any statistically increased risk of colorectal cancer in patients with ulcerative colitis over the general population.

The third classical concept has been that universal disease poses a particularly high cancer risk. And, in fact, it does. The incidence of colorectal cancer is highest for patients with pancolitis, but the risk is not restricted to patients with universal disease. As we see in Figure 2, patients with less than universal disease—that is, patients with left-sided disease extending up the descending colon or as far as

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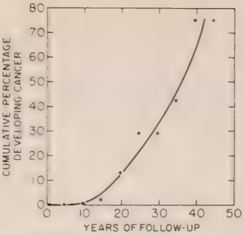


FIG. 1. Cancer incidence in ulcerative colitis. From Greenstein et al (1).

the midtransverse colon—have a time curve of cancer development parallel to that for patients with universal disease. The difference is that it seems to require about ten years longer for patients with left-sided disease to develop their cancers.

A fourth classical concept has been that patients who develop ulcerative colitis in childhood or in their teens carry an intrinsically higher risk of cancer than patients who develop their disease later on. It turns out, though, if one looks critically at the data, that it is the total duration of disease and not the age of onset that makes the difference. In Figure 3 we have attempted to separate these two factors from each other (1). Looking along the axis for age of onset of colitis we find that whatever the duration of disease has been, differing ages of onset do not appear to influence the incidence of cancer. But shifting our focus 90° and plotting the cancer incidence according to the duration of the colitis, irrespective of the age of onset of the disease, we find that there is a marked stepwise increase in cancer incidence with longer duration of disease. So it is disease duration, and not age of onset per se, that appears to be the determining factor in cancer risk.

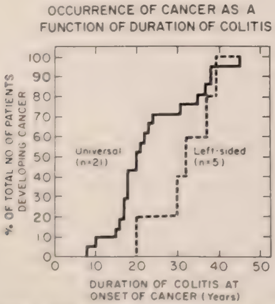


FIG. 2. Cancer in pan- vs. left-sided ulcerative colitis. From Greenstein et al (1).

Finally, the fifth classical teaching concerning ulcerative-colitis-related cancer has been that it has a worse prognosis. Indeed, a worse prognosis for the cancers might be predicted from some of their pathologic features (5). For example, colorectal cancers in ulcerative colitis are more often multiple than they are in de novo cancer. About 12% of ulcerative-colitis-associated cancers are multiple, as compared to about 3% in the noncolitis population. Moreover, they are more often extensive. They are also harder to suspect and detect, not only because the patients are young and often have symptoms of ulcerative colitis anyhow, but also because the cancers are more evenly distributed and even more shifted to the right in their anatomic distribution than are colorectal cancers in the general population. Figure 4 demonstrates these features of multiplicity, extensive spread, and uniform or even somewhat right-sided distribution.

But can we conclude from these pathologic characteristics that the overall survival rate is going to be much worse for colitis-related cancer than for de novo colorectal cancer? It turns out, not necessarily. To be sure, those patients with colitis-related cancer who have advanced disease when it is first diagnosed die very quickly. For this reason the survival curve initially drops very fast for patients with ulcerative-colitis-related cancer (Figure 5). In our series (5), patients with metastatic disease, representing half the total, are all dead within eighteen months. After that, however, the remaining 50% of patients survive very well. So once the patients are followed beyond two years or more, the overall approximate 50% survival for patients with cancer and ulcerative colitis is no worse than the record for colorectal cancer in the noncolitis population. This observation carries important implications for surveillance programs. There are, for example, some diseases, such as cancer of the lung or pancreas, where it has yet to be demonstrated that early diagnosis has any significant influence on long-term survival. But I think the implications are clear that for colorectal cancer, even associated with ulcerative colitis, early detection can have a profound impact on long-term survival.

Crohn's Disease and Colorectal Carcinoma

Let us now turn to the issue of cancer in Crohn's disease. Once again we start with the classical concepts of cancer risk. It is tradition-

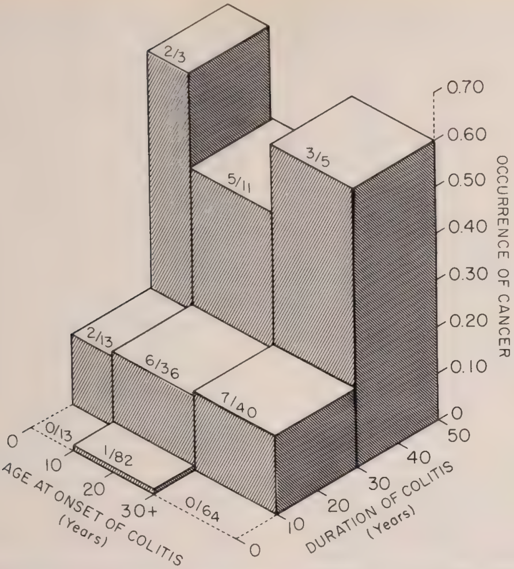
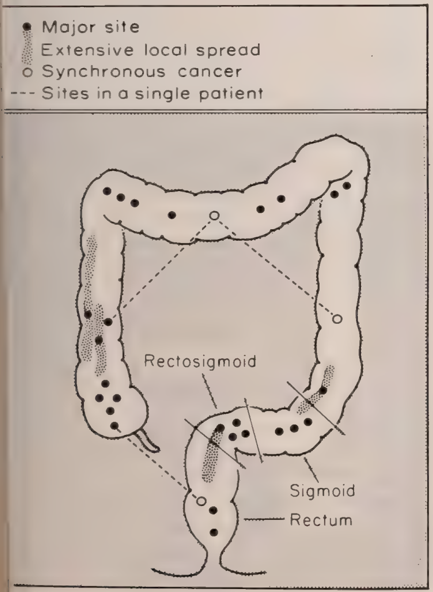
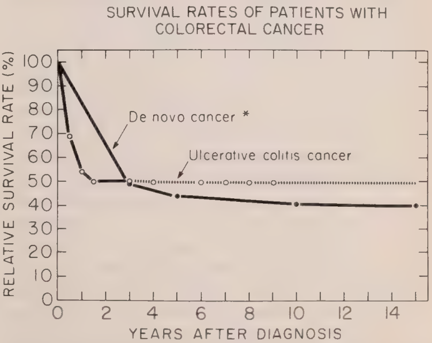


FIG. 3. Cancer incidence as a function of age at onset and duration of colitis. From Greenstein et al (1).


● Major site
▨ Extensive local spread
o Synchronous cancer
--- Sites in a single patient
Rectosigmoid
Sigmoid
Rectum

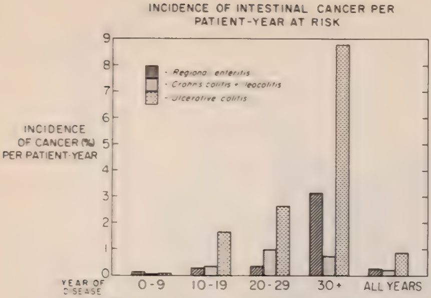
IG. 4. Anatomic sites of colorectal cancer in 26 of 267 pa- ients with ulcerative colitis. From Greenstein et al (5).

ally taught that there may be some increased cancer risk in Crohn's disease, but that the magnitude of this risk is nowhere near what we worry about in ulcerative colitis. This classical concept certainly appears true at first glance. As Figure 6 indicates, the incidence of gastrointestinal cancer per patient year, rising with increasing durations of follow-up for ulcerative colitis and Crohn's disease alike, is only about one-third the absolute magnitude among patients with ileitis and ileocolitis as it is for



** Modified from "End results in cancer", report no. 4, DHEW, 1972*

FIG. 5. Survival with and without ulcerative colitis. From Greenstein et al (5).



	0-9	10-19	20-29	30+	ALL YEARS
NO. OF CANCERS (A)	2 1 1	2 3 8	1 3 7	2 1 10	7 8 26
PATIENT-YEARS AT RISK (B)	1649 2347 1962	739 867 693	284 303 265	64 137 114	2736 3654 3034
A/B (%)	0.12 0.04 0.05	0.27 0.35 1.65	0.35 0.99 2.64	3.13 0.73 8.77	0.26 0.22 0.86

FIG. 6. Incidence of cancer. From Greenstein et al (6).

patients with ulcerative colitis (6). But what happens if we correct these incidence rates for age and sex distribution, comparing cancer incidence in this inflammatory bowel disease population to the expected cancer incidence in an age- and sex-matched standard population? If we conduct this kind of analysis, looking at the observed-to-expected ratio, we find that the risk for cancer of the colon in patients with Crohn's ileocolitis or colitis is overall about seven times greater than in the age- and sex-matched population (7). This increase is certainly less than the 26-fold ratio that one derives from similar calculations in patients with universal ulcerative colitis. But the 7-fold increase in risk of colorectal cancer for Crohn's disease involving the colon is not very different from the 8½-fold increase in risk that we have calculated for patients with left-sided ulcerative colitis. Now, if we consider that Crohn's disease of the colon is usually less than universal, often only segmental, and if we also allow for the fact that patients with Crohn's disease of the colon have not been recognized and followed with that diagnosis as long as patients with the diagnosis of ulcerative colitis, we might make a novel prediction. I am going to make such a prediction on the basis of no hard data, just on the basis of a hunch. My prediction is that in the 1980s, when cases of ulcerative and Crohn's colitis of similar anatomical extent are followed for similar durations of time, the two diseases may ultimately prove to have similar increases in risk for colorectal cancer. That's only a hunch. We'll have to come back in about ten or twenty years and see what has actually happened.

Cancer of the Small Bowel

Up till now, we have been speaking only of colorectal carcinoma. What about cancer of the small bowel? When one conducts an analysis to compare the observed to the expected incidence of cancer of the small bowel in patients with ileitis, compared to an age- and sex-matched standard population, most series agree that the risk is increased over the general population 100-fold (7). The classical teaching on this subject has been that there is something about a bypassed loop that specifically heightens the risk for developing small bowel cancer. This concept may not be true, however. Let us look at the data. Of all the 50 or so cases of small bowel cancer in ileitis that are reported in the world literature, about 40% have occurred in bypassed loops. Why is the occurrence of cancer in a bypassed loop this common? To answer this question, we have to look once again, just as we did with ulcerative colitis, at the issue of *total disease duration.*

Total Disease Duration

In the Mount Sinai series of seven cases, we have analyzed the intervals from onset of Crohn's disease to performance of bypass surgery, and then from time of surgery to appearance of cancer in the bypassed loop (8). The data are shown in Figure 7. In three of these seven cases, it took 25 or 30 years or more after the performance of the bypass for the cancers to develop. Those bypasses had all been done within 2, 5, and 7 years of onset of disease. But what about the other four patients? They developed their cancers early—within 1 to 4 years of the construction of the bypassed loop. But what did these four "early" cases have in common? They had all had Crohn's disease for 15 to 40 years before the bypass was performed.

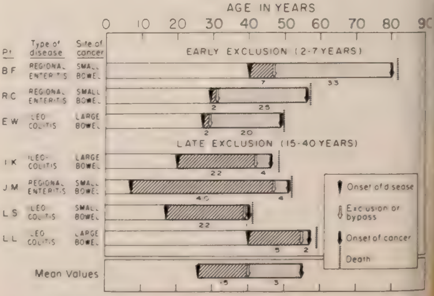


FIG. 7. Cancer in bypassed loops of Crohn's disease. *Designed by Adrian Greenstein.*

The common denominator, in other words, of all the cases of cancers in bypassed loops is that they were all cases of Crohn's disease of long duration. It requires at least 20 years of carrying ileitis in situ, unresected, before cancers are seen in the small bowel.

Now, who are the patients who have been going around for 20 or 30 years or more with small bowel continuously affected with ileitis? In large measure, these are patients who have had surgery in the early days, undergoing bypass without resection. Since more than two-thirds of patients with ileitis eventually come to surgery, the cohort of patients with bypass would obviously be overrepresented in that small population of patients who are carrying ileitis in situ unresected for 30 or 40 years, thus remaining at risk for small bowel cancer. In summary, then, to modify our classical concept, it is not the bypassed loop itself that puts the patient at risk for cancer; it is the long duration of the disease.

It seems, then, that the principal risk factor for cancer is the same in both Crohn's disease and ulcerative colitis—total disease duration. There is, however, an important difference between the gastrointestinal cancers that occur in Crohn's disease and those that occur in ulcerative colitis. In our patients with ulcerative colitis, 96% of the colorectal cancers develop in the areas of disease. By contrast, only about two-thirds of the gastrointestinal cancers in Crohn's disease occurred in a site of recognized gross disease; the others occurred elsewhere in the gastrointestinal tract (7). This finding harks back to a point raised earlier in this symposium concerning the distribution of Crohn's disease universally throughout the gastrointestinal tract, even in areas that we do not observe to be grossly involved. Is this a new idea, that patients with Crohn's disease can develop cancer outside diseased bowel? As noted in a preceding paper, nothing is new in this field. Cancer outside of involved segments of Crohn's disease has been described in at least four major reports of the 1960s. This realization brings us back to the title of this symposium: Inflammatory Bowel Disease: The First Fifty Years. I can't help wondering if we will ever discover anything in the *next* fifty years that wasn't already suspected by the giants of the *first* fifty years? Only time will tell!

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The Mount Sinai Journal of Medicine
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

The Challenges of Clinical Measurement

Thomas C. Chalmers, M.D.

In my years in hospitals and medical schools, I became convinced that the people responsible for administrative leadership were not as effective as they could be because they either had never been clinicians or clinical investigators or teachers, or because they rapidly lost those skills from lack of practice. I am determined that the only way to attempt to succeed in a position as godforsaken as the kind I occupy is to stay very active, or as active as possible, in research and teaching. Obviously, administrators cannot work in a laboratory, but there is one place in which they can find enormous amounts of untapped data, and that is the library. If one combines the availability of all those data with an interest in measurement, and with the availability of bright young medical students who are anxious to learn by doing and interested in presenting papers at national meetings, one can develop a program of analysis of how well things are done in the literature which will be both classifiable as research and teaching, and also keep one in a position to talk with the faculty and staff in a somewhat reasonable manner, as though one knew what was going on.

Diagnosis and Bias

The areas of diagnosis and therapy—and Crohn's disease is no exception—are areas in which there is an enormous opportunity for the ethical application of the scientific method to patient care. If one reviews the literature, one finds a tremendous lack of recognition of this opportunity by most of the doctors contributing to the clinical literature. The essence of the whole problem is one four-letter word: *Bias*. Bias is defined in the dictionary as "inclination of temperament or outlook, often such prepossession with some object or point of view, that the mind does not respond impartially to anything related to this object or point of view." That applies to diagnosis and therapy in spades.

To understand the ways in which bias can influence your observations or your clinical measurements, you have to appreciate what *observer error* is. Observer error can be defined as the differences between the observed findings and the truth. It embraces both sensitivity and specificity of the observation. Bias enters after consideration of the way in which observer error presents itself as *observer variability*. One form of observer variability is the documentable difference between two or more observations by the same person, the *intraobserver variability*. When the same people look at the same x-ray a month apart, do they see the same thing? Some percent of the time they don't. The error between two or more observers is called the *interobserver variability*. *Observer bias* is a distortion of observer variability that determines the direction of observer error and solidifies a difference as clinical error that may or may not be recognized.

In our program at Mount Sinai, which concentrates on analyzing various aspects of controlled clinical trials, we have not as yet looked at diagnostic papers in great depth. We do know that the great majority are badly done because the diagnostician does not appreciate these principles and rarely measures the everyday errors; I do want to remind people of their importance. I offer an example that, though not in the inflammatory bowel disease category, still serves as the easiest way to measure observer bias quantitatively.

Assume that you have a rapidly fibrillating patient, and you have two observers, good physicians; one of them measures the rate of the heart first at the apex through a stethoscope, and then at the wrist, and one of them takes the rate of the heart at the wrist first and then at the apex. You'll notice that the differences are striking, and if you replicate this, as I once did you will find a highly statistically significant difference. In other words, the size of the pulse

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deficit depends on which place is examined first. The person who examines the apex first counts more beats there and feels more pulses at the wrist. The person who feels at the wrist first counts fewer beats at the apex as well as the wrist. This is a highly effective demonstration of the occurrence of observer error, which is bound to occur whenever a patient is fibrillating at 150 to 200 times per minute, especially in palpating the wrist. Observer bias then occurs when the observer is attuned to the rapidity of the heart beat by listening first to the apex.

This is the neatest quantitative method of demonstrating what I mean. These principles apply to all diagnosis, of course, but one finds them very little emphasized in the literature. The principles are best illustrated in the table "Diagnostic Usefulness of a Test." In this common fourfold table the result of a test (positive or negative) is shown in the column on the left, and the confirmed condition (present or absent) is shown under the heading "truth," read vertically. When one has a test that is positive and the condition is present, one has a true positive; if the test is positive and the condition absent, one has a false positive. If the test is negative and the condition present, one has a false negative. Finally, if the test is negative, and the condition is actually absent, one has a true negative. The sensitivity of the test is A divided by $A + C$; specificity is D divided by $B + D$. Those two terms "sensitivity" and "specificity" are very seldom found in the investigation of methods of diagnosing disease. They are critical and should be used a lot more often.

Therapeutic Trials and Blindedness

Therapeutic trials have been the major source of our research emphasis at Mount Sinai. Again, I do not offer data directly applicable to inflammatory bowel disease, except for one example, although that is an area which we are planning to get to in greater depth at a later time.

Diagnostic Usefulness of a Test

Test Result	Truth +	 −		
+	A	B	+	Predictive Value $A/A + B$
−	C	D	−	Predictive Value $D/C + D$
	Test Sensitivity $A/A + C$	Test Specificity $D/B + D$		

I can report that one Mount Sinai student, Mr. Simon Chan, in his second year, is halfway through a study of the literature on inflammatory bowel disease. He has reviewed the ulcerative colitis randomized control trials, of which he found 40 in the literature, and the Crohn-Ginzburg-Oppenheimer diseases papers will be done next. So far they score about average quality.

One of the conclusions of our research into the validity of randomized control trials is that the word *double-blind* is markedly out of date. We are now talking about sextuply blinded studies; I imagine only the first three of these methods of blinding—randomization blinding, patient blinding, and physician blinding—are at all well known.

The randomization process has got to be blinded. You must not know when you access a patient for a study, and—because of the ease with which informed consent can be biased—when you obtain informed consent, which therapeutic group the patient will fall into. We have evidence to prove the validity of this concept. Yet only 40% of studies clearly state that the randomization process was blinded. It may be the most important blinding process of all. It is the explanation for the fact that historically controlled studies so often come up with conclusions which are more often positive and wrong than randomized control studies. And when the randomization process is not blinded, there is more often a maldistribution of pretreatment risk factors.

Patient blinding is done in 76% of the more than 300 studies that we have reviewed, and physician blinding in toto in 64%. Many people do not realize that in situations where the physician caring for the patient cannot be blinded, it is still possible to blind some observers who are gathering endpoint data. In other words, the physicians who are making the critical decisions on whether one therapy is better or worse than another can be blinded, even though those taking care of the patient may not be.

The fourth kind of blinding is one that is grossly neglected, although we do not yet have data on how serious the effects may be. In studies in which the blinding of therapies is absent or imperfect, it is rare that patients are removed either during the study or after the analyses start, with a lack of knowledge of which group the patient was in, or how well the patient was responding when the decision was made. Yet, once you accept as the sine qua non of a randomized control trial that only chance should determine which therapy the patient receives, and then you allow the removal of patients on some basis other than chance before you do the analysis, to that extent you destroy the randomization and destroy the validity of the statistical tests which are then applied to determine whether or not the differences are significant.

The fifth sort of blinding is blinding investigators as to trends; 21% of the papers did this. We think this is critically important, especially in long-term, large-scale studies. If patients are continuously being admitted and if there are withdrawals, whether or not the investigators know or suspect the trends will have a profound influence on their activities. Bias instead of chance may determine the final makeup of the treatment groups. One develops a situation in which patients who have less and less hope of being helped get into a study if there is a trend in favor of one therapy or the other. Simultaneously the patients who are likely to be helped are put in the category of refusing to join the study, and they are then treated with the treatment that is ahead—even though that treatment may, in fact, turn out not to be the best. There are difficult ethical problems about this. I think the only way they can be solved is to have an unbiased group of statisticians and clinicians looking at the data on a regular basis and declaring when the study should be stopped for the sake of the people in the study, as well as for the sake of other people who are not in the study but have the disease in question. Informed consent documents should describe this process.

Finally, the sixth type of blindedness: only 10% of the papers we reviewed included blinding of the biostatisticians when they were doing the analyses. This is obviously not possible much of the time, but it is important. The best example of that is the University Group Diabetes Program study, in which biostatisticians who originally worked on the study came up with one conclusion, and then other biostatisticians hired by people who sold the drugs came up with another conclusion. Obviously, that was an application of observer bias to the interpretation of what seemed to be the same data, so that if there is a possibility of distortion in the selection of tests to be done, or interpretation or expansion of the data, then it is important that the people making those decisions be relatively blinded as to which is which.

In the course of our analyses of these papers we developed a scoring system which we thought was relatively useful in predicting which studies were well done and which were not. We had the hope, and still have the hope, that this scoring system will enable one to look at any paper, whether it does or does not have the conclusion of interest to the investigator, and put some weight on how well the study was done in a quantitative manner. But because quite often we did not know the universal truth, we did not know whether a therapy really does or does not work, it was hard for us to correlate the quality of the study in a quantitative manner with the truth. We have only an approximate idea of what constitutes an excellent study. Most studies in a wide variety of fields cluster around 40% to 50% of the quality that they could have in the design of the protocol, and that record has largely to do with the blinding element, but also with how well the patients and therapies were described. Whether the researchers kept a log of rejected patients so that the reader can refer back to that, whether they calculated Alpha and Beta beforehand, whether they tested for patient blindedness, and whether compliance was measured were also scoreable items. The average scores for quality of statistical analyses were rather poor, averaging 29%. There were commonly missing elements, such as confidence intervals, time-related or regression analyses, giving both the P-value and the statistic on which it is based, and doing a retrospective Beta calculation in the absence of confidence intervals for a negative study.

Summary

My message about measurement is that it has to be done in clinical research for the data to be reliable; and it has to be done much better, and with much more scientific quality than it has been in the past, if physicians are to have reliable data on the relatively better diagnostic procedures and therapies which are rapidly proliferating.

The Mount Sinai Journal of Medicine
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

The Role of Corticosteroids

Samuel Meyers, M.D.

Corticosteroids are widely used for the therapy of inflammatory bowel disease. They have been successful when administered parenterally, orally, or by rectal instillation. Their efficacy in ulcerative colitis has been supported by several controlled placebo studies (1–3). Less reliable methods of analysis suggest their usefulness in Crohn's disease, although one controlled trial has supported the use of prednisone (4).

The National Cooperative Crohn's Disease Study reported prednisone to be superior to placebo in inducing and maintaining improvement (4). Sixty percent of subjects were successful with prednisone compared to only 30% for the placebo group. Prior uncontrolled reports generally agreed that corticosteroids produced short-term benefit but most suspected there would be no alteration in the long-term course of the disease (5–7). In the national cooperative study the anatomic disease location was important (4). Prednisone was superior to placebo when the disease involved the ileum or ileum and colon. It was not better when only the colon was involved; however, this group was small and definitive conclusions may not be possible. Among those responding to prednisone, therapy continued superior to placebo during 24 months of a reduced dosage maintenance period. Prednisone was not effective in preventing relapse or recurrence among patients after extirpative surgery or with inactive disease at entry. The use of prednisone or any corticosteroid must be tempered by the severe adverse effects which may result, as well as a suspicion by many that such effects are associated with an increased need for surgery, an increased mortality rate, and a significant incidence of serious Crohn's disease complications (8).

Controlled Trials of Corticosteroids

The remainder of my discussion focuses on a review of the controlled trials which have defined the use of corticosteroids in ulcerative colitis.

Truelove in 1958, in a double-blind trial, reported the superiority of hydrocortisone administered in a rectal drip over placebo for mild or moderate attacks of ulcerative colitis (3). Although initially systemic absorption was thought to be negligible, it may in fact be 30% or more of the administered dose (9). There may also be a beneficial role of combined local and systemic corticosteroids in more severe cases.

Truelove and Witts in 1955 treated 109 subjects with oral cortisone (100 mg daily) for six weeks and 101 with placebo (2). Cortisone was superior, and especially so for those with the first attack of the disease. The two groups did not differ in complications, although those on cortisone suffered more from pyogenic infection. Lennard-Jones et al in 1960 then confirmed the superiority of oral prednisone over placebo (10).

Thus everyone came to know steroid therapy as useful in active ulcerative colitis. True, the number of randomized, double-blind clinical trials is small, and these studies contain clear limitations. Yet even less is known about the patient with severe ulcerative colitis. The rectal instillation study of Truelove (3) and the prednisone data of Lennard-Jones et al (10) pertain only to the mild or moderate cases. Truelove and Witts (2) showed oral cortisone to be less favorable in severe cases, especially those in relapse of established disease. It appears that cortisone is worthy of a trial in all patients suffering from ulcerative colitis, regardless of the severity of the illness. It is also clear that the ideal patient for cortisone therapy is one undergoing a first attack, while the disease is still mild.

Finally we must consider the role of parenteral steroids in more fulminant cases or those with toxic megacolon. The use in these patients has been a matter of great debate but little study. Our own collective experiences must be drawn upon. Because most patients seen by us at Mount Sinai have developed their toxic dila-

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tion in the course of steroid therapy, corticosteroids must be maintained. Patients not promptly responding or those with clonic perforation or suspected perforation, whether on steroid therapy or not, require prompt surgical attention. In the small remaining number of patients who develop toxic dilation of the colon without prior corticosteroid therapy, it may be rational to add steroids to the present-day vigorous supportive medical program, provided failure to respond promptly does not lead to progressive delay in performing colectomy and ileostomy.

ACTH and hydrocortisone are both commonly used as parenteral therapy for severe ulcerative colitis. It has been suggested that ACTH is the superior of the two, but the issue remains controversial. Kirsner et al reported the largest clinical experience, consisting of 240 patients treated over seven years (11). They concluded that intravenous or intramuscular aqueous ACTH was the most effective corticoid therapy. Other small clinical series, however, did not confirm the superiority of ACTH (5). In a randomized controlled study of 169 subjects, Truelove and Witts (1) compared intramuscular ACTH-gel (80 units daily) to oral cortisone (200 mg daily). Both agents seemed to have similar efficacy overall and for a first attack, but ACTH appeared somewhat more effective for those with a relapse of established colitis. This apparent benefit of ACTH was offset by a higher relapse rate during the subsequent year. Powell-Tuck et al (12) in London compared intravenous hydrocortisone (400 mg daily) to intramuscular ACTH-gel (80 units daily) among 16 patients. Both agents were of similar efficacy but hydrocortisone was said to be the superior agent for those previously receiving corticosteroids.

The first direct comparison of intravenous ACTH and intravenous hydrocortisone was performed by Kaplan et al in New Haven (13). They studied 22 patients, in a prospective, double-blind manner, administering intravenous hydrocortisone (300 mg daily) or ACTH (40 units daily). The authors concluded that both agents were equally effective. Hydrocortisone, however, tended to be superior for patients who had been receiving corticosteroids prior to the study.

With Sachar and Janowitz, I studied 66 patients with severe ulcerative colitis in a prospective randomized clinical trial (14). They received either 120 units per day of intravenous ACTH or 300 mg per day of intravenous hydrocortisone. Patients were separately stratified depending upon whether they had received previous oral corticosteroids (Group A, 35 patients) or whether they received no such prior treatment (Group B, 31 patients). Fourteen of 34 patients (41%) achieved remission with hydrocortisone, compared to 14 of 32 (44%) receiving ACTH. In the B group, however, the proportion of patients entering remission was greater with ACTH than hydrocortisone (63% vs 27%, $p < 0.05$). The opposite trend was observed in the A group, in which hydrocortisone appeared more effective (53% vs 25%, $p = 0.06$).

Our study is thus the second direct controlled comparison of intravenous ACTH and intravenous hydrocortisone in the treatment of ulcerative colitis. Like Kaplan et al (13), we also prospectively stratified and separately randomized those patients receiving or not receiving prior steroids. In addition, we have introduced four new features to the experimental design. First, we restricted the study to patients with ulcerative colitis, in order to achieve more uniformity of the patient population. Second, for the same purpose, we established in advance specific clinical criteria of disease severity that would determine eligibility for entry into the study. Third, to ensure that any benefits of therapy would not be obscured by intermittent doses, we gave medications continuously over 24 hours. Finally, in an effort to achieve more statistically significant results, we resolved to study a much larger series of patients.

Our results indicate that the presence or absence of prior steroid therapy appears to be a determining factor in the preferential response to either ACTH or hydrocortisone. Previously treated patients responded better to hydrocortisone, whereas previously untreated patients did better with ACTH. This is the same conclusion reached by the New Haven (13) and London (12) studies. Of our patients entering remission with initial therapy, 71% continued well at one-year followup.

An obvious question is whether the relatively poorer effectiveness of ACTH compared to hydrocortisone in Group A might be attributable to impaired adrenal responsiveness among these patients who had received prior steroids. This explanation is not supported by our endocrinologic data. Mean serum cortisol levels were similar with either ACTH or hydrocortisone therapy, whether or not the patients received prior corticosteroid treatment. On the other hand, there may be other adrenal factors besides cortisol that play a role in the therapeutic outcome. Perhaps relative sluggishness in the production of these other factors by the adrenals of previously treated patients was partly responsible for their poorer therapeutic response to ACTH. The dehydroepiandosterone-sulfate data, however, do not provide support for this thesis. Mean serum levels were virtually identical among those patients receiving ACTH or hydrocortisone, regardless of prior steroid therapy.

On the basis of our data, we can recommend that patients hospitalized with severe attacks of ulcerative colitis be treated with intravenous hydrocortisone if they have been receiving prior corticosteroid therapy and with intravenous ACTH if they have not. It remains to be determined whether higher doses of either medication, or different schedules of treatment, would result in any increased therapeutic benefits.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

The Role of Immunosuppressives

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It was inevitable in the days when all diseases of unknown cause were being considered as possible autoimmune phenomena that treatment of inflammatory bowel disease with an immunosuppressive drug should be attempted. Both Crohn's disease and ulcerative colitis had been shown to be associated with abnormalities of the immune system, humoral and cell-mediated. It was Bean, an Australian, who first reported his success with 6-mercaptopurine in the treatment of ulcerative colitis (1). Later, others tried azathioprine, and early successes in the treatment of Crohn's disease were particularly exciting (2).

In the late 1960s at The Mount Sinai Hospital, when ulcerative colitis was still more prevalent than Crohn's disease, I was particularly frustrated by the poor prognosis of children with ulcerative colitis. Influenced by these early reports, Nathaniel Wisch and I treated 14 ulcerative colitis patients with 6-mercaptopurine (6-MP) when therapy with corticosteroids and sulfasalazine had failed but absolute indications for surgical intervention were lacking (3). Eleven out of 14 improved. When the series was increased to 25 patients (4), 15 did very well for long periods, and 8 improved, while 2 required surgery. We learned that toxicity was minimal, and the drug could be used safely for years. Most impressive were the remissions in young people; 13 children who had been incapacitated with ulcerative colitis and steroid complications were treated for a mean of 36 months and followed for 15 to 60 months. In six the response was excellent and nine did well without steroids for 7 to 43 months. Eight children grew and developed while receiving the 6-MP, including five with earlier growth retardation.

The time had come for double-blind studies. Efforts were then directed toward patients with Crohn's disease (which was increasing in incidence), whose course was unrelenting. There was less enthusiasm for trials of drugs considered carcinogenic for ulcerative colitis, which in itself was potentially carcinogenic but could be cured by total proctocolectomy.

The 6-MP was favored over azathioprine because our hematological colleagues had already accumulated a large experience in the use of this drug in the treatment of leukemia, because there had been no cases of carcinoma or lymphoma developing in the course of treatment of any disease with 6-MP, and because we had gained experience with the use of this drug in the earlier reported cases of ulcerative colitis. The results of earlier controlled studies have been variable, ranging from unequivocal benefit to no advantage (5). The drawback of many of these studies has been either the small number of patients evaluated or, more important in this chronic illness, the limited duration of the treatment period.

In 1970 my colleagues and I initiated a long-term double-blind randomized crossover study to determine the effectiveness of 6-mercaptopurine versus placebo in patients chronically ill with Crohn's disease (6). Eighty-three out of 700 patients seen in private practice fulfilled the criteria; all were considered failures with sulfasalazine and/or steroids, the latter having been used many times and for long periods. Management of the study drugs and subsequent management of the 6-MP have been described elsewhere (6, 7). In most cases, active disease had once again been brought into remission with high-dose steroid therapy. Forty-three of the 83 patients had already had one or more bowel resections and suffered with recurrent Crohn's disease, some with complications. Specific goals were established for success in each case, in keeping with the way patients with Crohn's disease are usually managed. The most common examples of these goals included elimination of primary bowel symptoms, reduction and cessation of steroids and healing of fistulae. Other goals were prevention of recurrent

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small bowel obstruction, elimination of a right lower quadrant mass, and improvement of malabsorption. Usually there was more than one goal for each patient.

Seventy-two patients completed at least the first year of the study; 36 received 6-MP and 36 the placebo. Of the 36 receiving 6-MP, 26 (72%) improved ($p < 0.001$), whereas of the 36 receiving placebo, only 5 (14%) improved; these differences are very highly significant (6). Thirty-nine completed the study with crossover. Twenty-nine improved in one of the two years; 26 were taking 6-MP and 3 placebo. The proportion who improved with 6-MP was 66.7% (26/39), whereas the proportion who improved with placebo was 7.7% (3/39). This combination of results was of still higher statistical significance (6).

In regard to specific goals, the following observations were made. Steroids were discontinued with a coincident improvement in 53% during the year the patient received 6-MP, and were significantly reduced, but not stopped, in another 22%. Fistulae were totally closed in 31% (nine patients) of those receiving 6-MP and were partially healed in another seven. The types of fistula which responded best to 6-MP were the abdominal wall and the internal (enteroenteric), but there was a 50% response rate in the perirectal and rectovaginal fistulae as well. There were instances of clearcut response to 6-MP with resolution of abdominal mass, improvement in malabsorption, and relief from recurrent small-bowel obstruction, although this last group in general seemed the least likely to respond. Those patients with colonic involvement (colitis and ileocolitis) fared better than patients whose disease was limited to the small bowel, and those treated prior to any surgery had an advantage over those who had already undergone one or more resections.

The mean time of response to 6-MP was 3.1 months, with a range of two weeks to nine months. Though 10% responded in one month r less and 68% had responded by three months, some of the patients who ultimately responded the best of all did not begin to show improvement until as many as 10 months had passed.

TABLE I

bservations on Worrisome Concerns Attributed to 6-MP and Azathioprine

Concern	Observation
eratogenic effects	none
ersistence of chromosome breaks	none
eproductive capacity	?
ymphomas in transplant cases	3%–4%
alignancy in transplant cases	16%
alignancy with rheumatoid arthritis	11/20,000
alignancy with IBD	rare

TABLE II

Effect of Discontinuing 6-MP in Crohn's Disease after Initial Improvement (32 cases)

Further improvement	1 (3%)
Maintenance of improvement	5 (16%)
Relapse	26 (81%)

The side actions and toxicity occurring in the course of treatment with 6-MP have been described elsewhere (6, 7). Those which by experience seem temporally related to the drug are: leukopenia, bone marrow depression, upper respiratory infection, herpes zoster, pancreatitis, fever, nausea, pneumonia, cytomegalovirus, hepatitis.

No deaths have occurred in patients with either Crohn's disease or ulcerative colitis treated with 6-MP in our experience. Table I lists those observations to date on the most frequently expressed concerns which cause pediatricians and gastroenterologists to hesitate in using immunosuppressives despite situations in Crohn's disease otherwise warranting use of these drugs.

Since 6-mercaptopurine is effective in a large percentage of patients with Crohn's disease, several questions logically arise. How long should the drug be continued? When should it be stopped? If it is stopped, will it again be effective in the event of relapse? Preliminary data are available on 52 patients after improvement on 6-MP during the double-blind study (20 who continued the 6-MP and 32 who stopped it) as well as the results of restarting the drug in 16 after relapse. Of the 20 who continued the 6-MP, improvement was maintained or even increased in 19 after 18 to 77 months (mean, 37 months). Of the 32 who stopped taking 6-MP, relapse took place in 26 (Table II), but in only half of these did the recurrent symptoms appear within six months (Table III). In the patients in whom the 6-MP was restarted after relapse, not only did the Crohn's disease improve in all instances, but the mean time of response was significantly less for the second course of therapy than for the first: mean 1.5 months as compared to 3.5

TABLE III

Time to Relapse after Discontinuing 6-MP

Time	Number (%)
Less than 1 month	6 (19%)
6 months	17 (53%)
1 year	23 (72%)

TABLE IV

6-MP: Time to Response in First and Second Treatment Course

Response Time	First Course	Second Course
Immediate	0	8 (50%)
1–2 months	9 (50%)	5 (81%)
3–6 months	5 (87%)	3 (100%)
Over 6 months	2 (100%)	0
MEAN RESPONSE TIME	3.5 months	1.5 months
RANGE	(1–8 months)	(.5–4 months)

months (Table IV). The drug was restarted after 0.5–42 months; average, one year.

The differences between the results of this study and the National Cooperative Crohn's Disease Study (8) warrant comment since we conclude that one immunosuppressive drug (6-MP) is highly effective, in contrast with another (azathioprine) which was reported to be ineffective (9). Two major differences in study design provide the most likely explanation. In the National Cooperative Crohn's Disease Study, all other drugs had to be stopped at the time of randomization to the treatment drug. If the patient's disease was controlled or modified by prednisone and this drug was suddenly withdrawn, recurrence was favored. This is particularly so when it is suspected that the azathioprine could not, for some time to come, substitute for the prednisone in maintaining some modification of the course of the Crohn's disease existing at the start of the study. In the Lenox Hill-Mount Sinai study, patients receiving steroids at the outset continued and reduction of the drug was monitored as one of the criteria of response. This is more in keeping with the natural course of Crohn's disease and the way it is managed in private practice.

Though probably not of similar importance to the two differences outlined above, it must also be considered that 6-MP and azathioprine are not the same drug. In vivo, azathioprine is metabolized to 6-MP, which may be the more effective agent.

TABLE V

Complications of Crohn's Disease: Responses to Purinethol

Outstanding Responses	
Chronic small and large bowel obstruction associated with ileorectal abscess and fistula	4
Recurrent jejunitis proximal to anastomosis	3
Rectovaginal fistula	4
Abdominal wall fistula	3
Complex perirectal fistula	2
Recurrent ileitis in an ileostomy	1
Short bowel syndrome, malabsorption	1
Poor Responses	
Recurrent small bowel obstruction	9
Jejunal stricture	2
Peri ileostomy abscess	2

Others have conducted a double-blind withdrawal trial proving that azathioprine was successful in maintaining remissions in Crohn's disease (10).

In some Crohn's disease situations the response to 6-MP has been outstanding. In others, observations have shown an unsatisfactory response (Table V). Other general observations and concerns regarding patients with Crohn's disease managed for extended periods are noted in Table VI.

It is now more than twelve years since the circumstances of the period favored trials of immunosuppressive drugs in the treatment of Crohn's disease over ulcerative colitis. It does not seem that the then-existing concern about provoking the predisposition to carcinoma of the colon with azathioprine or 6-mercaptopurine was warranted. Reports of carcinoma occurring in ulcerative colitis patients receiving these drugs have been rare and in each instance fit well with the natural course of the disease independent of these drugs (11, 12). In fact no reasonable proof of carcinogenic complications in any nontransplant cases treated with immunosuppressive drugs has been found (13). Preliminary studies by the international agency for re-

TABLE VI

Crohn's Disease: Treatment with 6-MP

	Number of Patients	
Observations and Concerns	On 6-MP	Off 6-MP
Prolonged remissions	41	6
Recurrences after remission	27	8
Prophylaxis after second surgical resection	6	
? Patient compliance	5	
Complications causing concern	4	

search on cancer suggest that even at doses of immunosuppressives used in transplant cases, in which azathioprine has been considered carcinogenic, 6-mercaptopurine has not (14). Meanwhile, I and many of my colleagues in the United States and other countries have continued to treat ulcerative colitis patients with 6-MP when other treatment has failed, when there was as yet no absolute indication for operative intervention, or when the patient has been provided with that option prior to consideration of surgery. The results have been impressive and suggest that the response rate in ulcerative colitis is similar to that in Crohn's disease. Even if the response rate is not as high, there are a sufficient number of obvious responses to suggest a subgroup of ulcerative colitis patients who respond to immunosuppressive drugs. Controlled trials of immunosuppressive drugs in treatment-of-choice patients with ulcerative colitis are warranted with consideration of the known rate of response and the need for temporary use of steroids.

Summary

The drug 6-MP is effective in the treatment of Crohn's disease for long periods of time, and it is reasonably safe, particularly when considering the chronic unrelenting course of the disease in so many young people. Though a relapse may be expected after cessation of the drug, relapse may not occur for a long time; it may occur in a milder form not requiring reintroduction of 6-MP, and if 6-MP is again necessary it is likely to be effective. It should be used in the treatment of Crohn's disease when sulfasalazine does not prevent relapse, when steroids cannot be reduced or stopped, and when steroids must be frequently reintroduced. Ideally it should be used before complications ensue. Perhaps when we feel more comfortable with its use it might be justified even earlier in the course, when the disease is still considered mild.

There is no longer justification for the belief that predisposition to carcinoma in long-standing ulcerative colitis warrants postponing double-blind trials of 6-MP similar to those conducted in Crohn's disease.

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The Mount Sinai Journal of Medicine
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

The Surgical Approach

Isadore Kreel, M.D.

In any discussion of the management of inflammatory bowel disease, the role of surgery, both its extent and its timing, are controversial. This is so for several reasons. In ulcerative colitis, the disease involves the entire colon and rectum. The definitive resection of the disease classically requires a permanent ileostomy. In Crohn's disease, the underlying problems for the surgeon are not just the multiple potential sites of involvement, but the high incidence of recurrence after resection.

Indications for Surgery in Colitis

Indications for surgery in colitis can be summarized as follows:

1. Intractability: Failure of management without operation.
    - A. Growth retardation in children.
    - B. Inability to function socially and/or financially.
    - C. Complications of steroid therapy.
2. Fulminating colitis or toxic megacolon.
3. Perforation
4. Unremitting hemorrhage.
5. Stricture.
    - A. Obstruction (Crohn's disease).
    - B. Carcinoma cannot be excluded.
6. Carcinoma or high probability of cancer.
7. Anal or perianal complications.
    - A. Stricture (rare).
    - B. Severe abscess or fistula formation.
8. Unremitting cutaneous or extracolonic manifestations (arthritis, uveitis, liver disease, pyoderma, erythema nodosum, and so on).

The emphasis is primarily on ulcerative colitis, but it is largely valid for Crohn's colitis. You will note that there is a significant difference between the ordering of these factors here and the presentations made by other speakers. I think that there can be agreement on numbers 3 and 4. Free perforation, documented sealed perforations, or unremitting severe, progressive, and life-threatening hemorrhage constitute valid and unarguable indications for surgery. It is really on numbers 1 and 2 that there is a difference of opinion. The reason that there is a difference of opinion is that one is measuring a rather poorly defined condition, "intractability." Our experience is that if a youngster misses time from school each year, if a young adult cannot hold a job, if a young adult cannot have any sort of a social life, or if a patient is beginning to suffer overt and threatening complications of steroid therapy, the disease is intractable and surgical treatment must be considered. The question of stricture is open to discussion. While fixed, obstructing strictures may be an indication for surgery, there are some strictures which do appear to open up. The danger of a stricture being in fact a carcinoma is not as valid today, with the availability of well-controlled and well-performed endoscopy and biopsy. I am sure that there will be further discussion of this problem.

Coexistent carcinoma is an absolute indication. The high statistical probability of malignant change has been discussed. Those patients who previously did not have dysplastic changes who develop them under observation have a reasonable indication for surgery on the grounds that they are at significant risk for malignant transformation.

Anal and perianal indications are relatively uncommon in ulcerative colitis. They are today uncommonly the indication for colectomy in Crohn's disease. I think that we have been a little too conservative in the surgical management of perianal complications in Crohn's disease. The classic teaching was that you tried as much as possible not to operate for fear of inducing either total sphincteric incontinence or a chronic nonhealing wound in the perineum. I think that the simple unroofing of perianal abscesses in these diseases remains a valid operation. I think that the Parks operation is one which must seriously be considered for complex

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fistulae. I am particularly impressed with Dr. Korelitz's report that in addition to simple drainage, the use of immunosuppressive agents may cause a significant subsidence of perianal disease. Extraintestinal complications are a relative indication, and these have been extensively discussed by Dr. Present.

Indications for Surgery in Crohn's Disease

In Crohn's disease the indications for surgery are as follows:

. Perforation.
. Obstruction.
. Abscess.
. Fistula.
. Intractability.
. Anal lesions.
. Probability of carcinoma.

Except for free perforation, these indications are relative. Free perforation into the peritoneal cavity in small-bowel Crohn's disease is uncommon, in part because the disease is characterized pathologically by thickening rather than hinning of the bowel wall. The disease is worse n the mesenteric side; perforation occurs beween the leaves of the mesentery, forming inramesenteric abscesses. The intramesenteric bscess may perforate free into the peritoneal avity, a surgical emergency, or may perforate o the skin or into another viscus, that is, a fisula. In and of themselves, enteroenteric fistuas are not an indication for surgery. But enteroesical, enterovaginal, and enterocutaneous istulas may be disabling conditions, making he patient's life miserable, and rehabilitation ecomes a major problem. Fistulization of these orts, if they are treatment failures, constitute a alid indication for surgery. Abscess formation hich does not respond to antibiotics is an inication. I specifically mention antibiotics and ot steroids, because steroids may suppress the ever, suppress the local peritoneal findings, hile the infection continues to rage in the cener of the abscess. And because of what is nown about the effect of immunosuppressants n white cells, I am greatly concerned with hether a similar risk attends the use of imunosuppressants with frank, intra-abdominal bscesses. These comments refer to actual abcess, not inflammatory masses made up of dematous bowel, edematous mesentery, and dematous lymph nodes. Questions of intractability, anal lesions, and probability of carcinoma are discussed at length by other contributors.

Choice of Operation

The question of what operations should be performed arises. In ulcerative colitis the yardstick against which every other procedure must be measured is complete removal of the colon and rectum, and formation of a standard Brooke-type end ileostomy. It is a curative operation in ulcerative colitis, and for most patients provides a readily manageable stoma. Subsequent contributors discuss options in stomas, including the continent ileostomy and total abdominal colectomy and mucosal proctectomy, preserving an intact muscular type of rectum, with restoration of intestinal continuity to the anus. These procedures may well cause the surgical indications to be widened, if they provide a curative operation in ulcerative colitis without the disabilities of the usual ileostomy. How long we will maintain a young person on immunosuppressants or steroids with attendant complications, or how long we will allow a person to suffer the chronic disability of the disease may be shortened as these alternate techniques are perfected. The question of what operation to do for Crohn's disease has been discussed at length. There is fairly unanimous thinking today in surgical circles that the best operation is to remove the diseased segment and restore intestinal continuity if possible. Other operations, for example temporary bypass with exclusion, or temporary diversion, are really holding techniques until the diseased segment can be removed with restoration of intestinal continuity where possible.

Two other situations should be mentioned in the surgery of Crohn's disease. Firstly, how much should you take out? Our thinking in this institution is to remove the obvious disease only and clear it by a few centimeters on either side. We have found very little help in predicting recurrence from frozen section study at the resection margins. We have obtained no improvement in our results from widely clearing the gross disease, as one might find in neoplasm. We have found no help whatsoever in extensive lymph node removal. Attempts to remove lymph nodes may put the blood supply to the entire small bowel significantly at risk.

Another technique we now use is in those patients with abscesses that are pointing to the skin. The teaching classically had been that one did not drain abscesses without diverting the fecal stream. Our recent experience is that this is not valid. For a patient with Crohn's disease, particularly of the small bowel, with an abscess, with the overlying skin becoming thin and red, we locally drain the abscess only, accepting the resultant small fecal fistula. The patient's clinical toxicity defervesces, the mass shrinks, the patient becomes well. Usually, on the same admission, a few weeks later, in a completely stable patient, we have been able to enter the abdomen in a clean, uncontaminated area, and do the definitive resection for the underlying intestinal disease.

To reiterate what has been said by another speaker, where there is coexistent hydronephrosis or hydroureter in Crohn's disease, we do not attempt a ureterolysis. Dealing with the intestinal component of the disease has been adequate. The hydroureter and hydronephrosis resolve.

The Mount Sinai Journal of Medicine
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Applications of Conventional Ileostomy

Gary I. Slater, M.D.

The use of an ileostomy, either as a sole procedure or in conjunction with other procedures, is an extremely important and commonly used therapeutic modality in the treatment of inflammatory bowel disease. The three common types of ileostomy in use at the present time are end ("Brooke" type), loop, and continent (Kock). This paper deals only with the end and the loop ileostomy.

Ulcerative Colitis

Ileostomies are an extremely important and standard part of the surgical management of ulcerative colitis. The indications for surgery in ulcerative colitis can be divided into elective and emergency. These indications are shown in Table I. The most commonly performed elective operation for this disease is total proctocolectomy with either end or continent ileostomy. Much less commonly performed operations that do not include a permanent ileostomy include colectomy with ileorectal or ileoanal anastomosis. Recently there have been several reports on colectomy with rectal mucosal stripping and ileoanal anastomosis. The large majority of procedures include a permanent ileostomy of some type. In addition, many of the procedures that do not utilize permanent ileostomy make use of temporary ileostomy (often of the loop variety) constructed for diversion. Emergency operations for ulcerative colitis all include some form of ileostomy—total or subtotal colectomy with ileostomy, or loop ileostomy in conjunction with decompressing transverse and sigmoid colostomies as described by Turnbull.

Crohn's Disease

In Crohn's disease, ileostomies are used much more selectively; indications for elective and emergency or urgent surgery are shown in Table II. The majority of operations involve resectional surgery with end-to-end anastomoses. Ileostomies are therefore necessary in only a small minority of cases. Those clinical situations that do require an operation which includes an ileostomy can be divided into two categories: elective and emergency (Table III). In elective situations, ileostomies are frequently performed in three types of patients with Crohn's disease. The first group includes patients with Crohn's disease of the colon, for whom ileostomies are performed in conjunction with colectomies in a similar fashion to those done for ulcerative colitis. In the second group of patients, ileostomies are performed as the sole procedure, usually as preliminary to a definitive resection in patients who are quite ill and debilitated or have very complicated disease. In the final group of patients, ileostomies are performed in conjunction with other complicated procedures, such as multiple resections or resections with significant contamination.

Series of 34 Patients

I and my colleagues Drs. Aufses and Kreel have had experience with 34 patients who were operated upon for Crohn's disease and had an ileostomy performed as either the sole procedure or in conjunction with other procedures. Patients who underwent elective total proctocolectomy and ileostomy were excluded. Both end and loop ileostomies were performed. The percentage of loop ileostomies has recently increased significantly, especially when the ileostomy was considered to be temporary. We have found that loop ileostomy functions as satisfactorily as end ileostomy. In addition, loop ileostomy is easier to construct and close.

The anatomic distribution of the granulomatous disease among the 34 patients was: ileitis, 13; ileocolitis, 19; and colitis, 2. The indications for surgery in this group of patients are shown in Table IV. In the emergency or urgent group, 17 of the patients had evidence of ob-

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vious peritonitis. In the elective situation, about one-half of the patients had their ileostomy performed in conjunction with another procedure and one-half had their ileostomy performed as the sole procedure.

TABLE I
Indications for Surgery in Ulcerative Colitis

Elective

Failure of medical management (intractability)
Growth retardation
Risk of carcinoma
Stricture
Carcinoma
Extraintestinal manifestations
Perianal problems

Emergency or Urgent

Fulminating disease
Toxic megacolon
Hemorrhage

TABLE II
Indications for Surgery in Crohn's Disease

Elective

Failure of medical management (intractability)
Growth retardation
Fistula formation
Perianal disease
Strictures
Cancer
Extraintestinal manifestations

Emergency or Urgent

Obstruction
Abscess formation
Perforation (free or abscess)
Fulminating disease
Toxic megacolon
Hemorrhage

TABLE III
Situations in which Ileostomy May Be Perfomed in Crohn's Disease

Elective

Sole procedure
- malnourished and/or debilitated patient
- with complicated disease
- severe perianal disease

In conjunction with other procedure
- ileoproctostomy
- multiple resections
- resection with contamination (pus, multiple fecal fistulas, etc.)

Emergency or Urgent

Abscesses (± perforation)
Free perforations
Acute intestinal obstruction
Anastomotic breakdown
Fulminant disease

Loop Ileostomy

Several cases are presented that illustrate some of the indications for loop ileostomy.

Case 1: Perforated Mesenteric Abscess. CP (Fig. 1) was a 40-year-old white woman who had undergone an ileocolic resection for terminal ileitis 23 years prior to the admission and had had several episodes of partial intestinal obstruction in recent years. She now had fever, a right lower quadrant mass, and signs of peritonitis. Exploration revealed localized perforation of a mesenteric abcess in the lower abdomen, as well as diseased bowel at the site of a previous anastomosis. Drainage of the abscess as well as a loop ileostomy were performed. Her postoperative course was satisfactory and she underwent an ileocolic resection four months later. Two months after the second procedure her ileostomy was closed. *Comment:* A resection and an anastomosis in a heavily contaminated field with a high probability of leakage was avoided by a rapidly performed loop ileostomy and drainage.

Case 2: Free Perforation. ER (Fig. 2) was a 32-year-old white man with a twenty-year history of ileocolitis beginning with a perirectal abscess. On admission he had abdominal pain, weight loss, and diarrhea. Contrast studies showed disease of the colon, the distal small bowel, and a duodenal-colic fistula. He was placed on hyperalimentation in an effort to prepare him for surgery, but suddenly developed acute peritonitis. Emergency exploratory laparotomy revealed free perforation of a severely diseased terminal ileum. A loop ileostomy, drainage, and exteriorization of the perforation was performed. He did well postoperatively and remained asymptomatic nine months later with his ileostomy still in place awaiting further surgery. *Comment:* Resection of the perforated ileum and adjacent diseased colon would have necessitated a difficult subtotal colectomy with a possible postoperative duodenal leak in this severely ill young man.

Case 3: Intestinal Obstruction. GQ (Fig. 3) was a 31-year-old man with a history of granulomatous disease of the terminal ileum and possible involvement of the sigmoid colon who now had acute intestinal obstruction and high fever. Laparotomy revealed almost complete obstruction at the terminal ileum and an inflammatory mass involving the sigmoid colon. A loop ileostomy was performed. Postoperatively, the patient recovered without complication. Upon further evaluation it was found that

TABLE IV
Indications for Surgery, 34 Patients

Emergency or Urgent		Elective	
Abscess (± perforation)	12	In conjunction with other surgery	
Free perforation	1	Ileoproctostomies	3
Obstruction	3	Multiple resections	1
Anastomotic breakdown	2	Resections with contamination	2
Fulminant disease	4	Sole procedure	
		Malnourished patients	6
		Perianal disease	1

there was no intrinsic disease of the sigmoid colon and an ileocolic resection was done. Subsequently, he had closure of his ileostomy without complications. *Comment:* Because of the uncertainty of colonic disease and the massive dilatation of the ileum, resection was not attempted at the initial exploration.

Case 4: Two Simultaneous Resections. LL (Fig. 4) was an 18-year-old white woman with a persistent fecal fistula after appendectomy. Approximately six months later she was found at surgery to have Crohn's disease of the ileum with an ileocutaneous fistula and an ileosigmoid fistula. She underwent an ileocolic resection as well as a sigmoid resection with loop ileostomy. Postoperatively she did well and had her ileostomy closed two months later. *Comment:* It was felt that the use of a loop ileostomy might reduce the postoperative complications in this patient who underwent two simultaneous resections in the presence of a fistula and gross contamination.

Case 5: Ileoproctostomy. AB (Fig. 5) was a 69-year-old man with a 27-year history of granulomatous colitis, who presented with a spontaneous fecal fistula originating in the sigmoid colon at an area of stricture. At surgery he was found to have disease of most of the colon (the

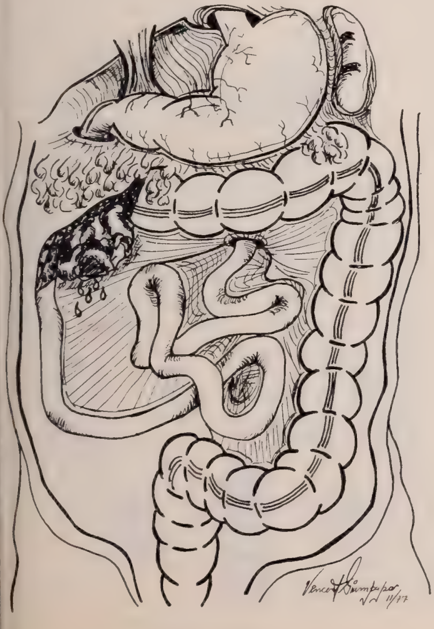

FIG. 1. Case 1.

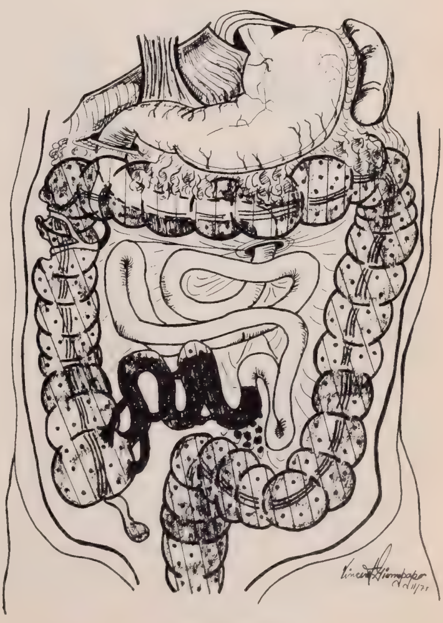

FIG. 2. Case 2.

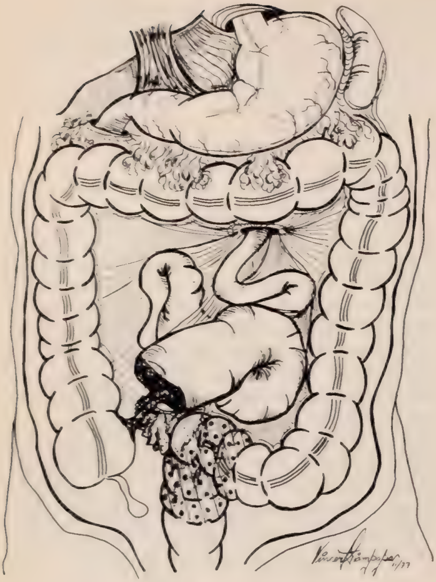

FIG. 3. Case 3.

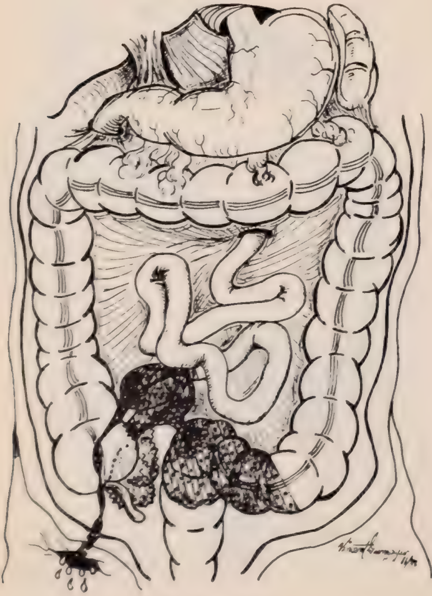

FIG. 4. Case 4.

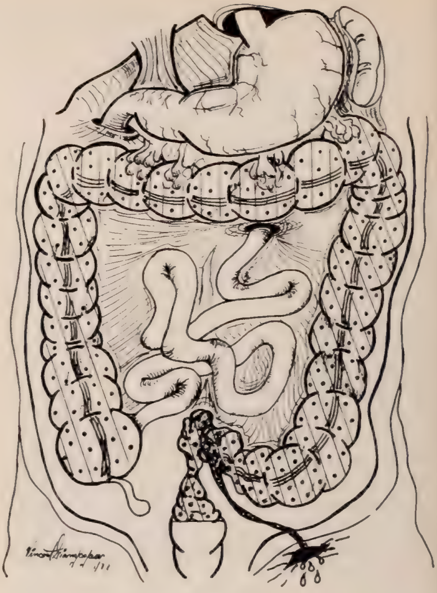

FIG. 5. Case 5.

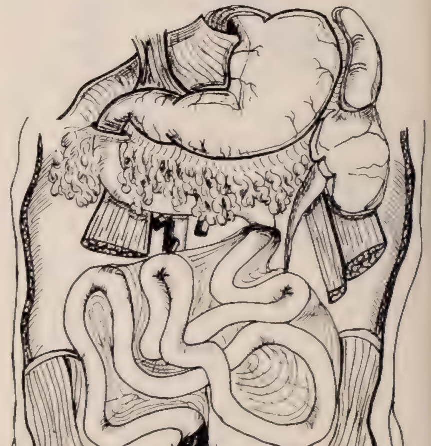

FIG. 6. Case 6.

rectum was spared) with a large inflammatory mass in the sigmoid. He underwent subtotal colectomy with ileorectal anastamosis and loop ileostomy. He did well postoperatively and eventually underwent closure of his ileostomy. *Comment:* Loop ileostomy was used as a diversionary procedure in this technically difficult ileoproctostomy.

Case 6: Debilitated Patient. MS (Fig. 6), a 50-year-old woman with ileocolitis who had previously undergone an ileoproctostomy, was admitted because of recurrent disease of the rectum as well as malnutrition and weight loss. Because of her poor medical condition she underwent a loop ileostomy rather than resection. Four months later, after her condition improved, abdominoperineal resection was performed, with conversion of her loop ileostomy to a permanent end ileostomy. *Comment:* The temporary ileostomy was instrumental in helping to prepare this woman for major resectional surgery.

Results

The results of treatment of this group of patients is shown in Table V. Six of the patients have had their temporary ileostomies converted to a permanent ileostomy. All of the other patients either have had or are planning to have their stomas closed, except for six patients who do not want further surgery at present. There were three deaths in this series, two in the postoperative period and one during an elective interval operation. The first patient was a 70-year-old woman with Crohn's colitis who had generalized peritonitis and bilateral pulmonary emboli. She underwent drainage of multiple intramesenteric abscesses and a loop ileostomy for an old perforation of a diseased sigmoid colon. She died of pulmonary insufficiency. The second patient was a 68-year-old woman who had a third operation for Crohn's disease which included an ileocolic and sigmoid resection. After a postoperative leak at the site of the sigmoid anastomosis, she underwent a loop ileostomy and drainage. She died postoperatively of continued sepsis. The third patient had previously had an ileostomy and subtotal colectomy performed for fulminant colitis and did well. He died after an elective abdominal perineal resection following the development of a liver abscess.

TABLE V

Results of Treatment, 34 Patients

Restoration of continuity planned or accomplished	10
Ileostomy closed	9
Conversion to a permanent ileostomy (± resection)	6
No further surgery	6
Died	3

Discussion

It is clear that the performance of an ileostomy remains an essential and important part of the surgical treatment of inflammatory bowel disease. In ulcerative colitis, ileostomy is used along with some form of proctocolectomy in the large majority of cases. In granulomatous disease, on the other hand, the need for an ileostomy is much less frequent. A great deal more judgment is necessary to decide which patients may benefit from an ileostomy, especially since an operation in this disease is not curative.

In the case of severe granulomatous disease of the colon and rectum, the choice of ileostomy and total proctocolectomy is usually obvious. If there is disease of the colon and upper rectum or possibly even some mild disease in the mid and lower rectum, an ileoproctostomy may be an acceptable alternative, with or without a temporary ileostomy.

We have found the use of a temporary ileostomy to be of particular importance in the management of difficult cases of Crohn's disease. Although end ileostomies can be useful in this regard, especially after subtotal colectomies, the use of a loop ileostomy has been even more helpful.

Ileostomies can be helpful in both emergency and elective surgery. In emergency settings, it can be used in situations where anastomotic procedures would be of great risk and where special anatomic and technical considerations make the necessary surgery particularly difficult and unsafe. In the elective situation, ileostomies have been used as the sole procedure in poor-risk patients that are thought to be too ill to undergo definitive surgery. The increased use of hyperalimentation recently has diminished the number of patients that can benefit from this procedure. Ileostomy can also be used in conjunction with definitive procedures when it is thought that there is an undue risk of postoperative complications such as leaks or abscesses.

In the large majority of cases in which ileostomies are constructed (except after total proctocolectomies), the ileostomy is considered to be a temporary procedure and not definitive therapy. We feel that the proper use of an ileostomy can significantly decrease the mortality and morbidity of surgery in Crohn's disease.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Experience with the Continent Ileostomy

IRWIN M. GELERNT, M.D.

This morning and afternoon it has been a little difficult listening to some of our physician friends telling us about some of their wonderful results, and how fewer and fewer people are coming to surgery. As a counterexample consider a patient with an easily seen carcinoma in the hepatic flexure. With very proper surveillance, barium enemas were done on this patient frequently, and a gastroenterologist followed the case. One year later, the carcinoma at the hepatic flexure was still obvious on x-ray. Why does this happen in the course of a disease which we have all been taught can be absolutely cured by total proctocolectomy and ileostomy? The reason it happens is that there is still a great deal of reluctance among patients, their families, and—even more problematic—most gastroenterologists to accept the need for a continuously worn appliance. This explains why we started evaluating the continent ileostomy some ten years ago, in the last decade of the past fifty years.

The continent ileostomy is constructed from the terminal 40 cm of the ileum. The last 10 cm is used for an outflow tract and nipple valve. Two 15 cm limbs are folded in a U-shaped pattern, and a suture line is placed along the antemesenteric border (Fig. 1A). The bowel is then opened along the suture line, and a second suture line is placed (Fig. 1B). The nipple valve is constructed by intussuscepting the terminal ileum in a retrograde fashion (Fig. 1C). Most of the difficulties with this operation come about because of slippage of the nipple valve. Changes made since Dr. Nils Kock's introduction of this procedure have improved the results a great deal. The nipple valve is reduced and the serosa is damaged with cautery (Fig. 1D), in an effort to achieve firm serosal bonding once the nipple is again reintussuscepted. The difficulty in securing the mesenteric portion of the valve was obvious as soon as we began doing this procedure, in Fall 1972, and by our third patient, recognized that this was the weak point. The diagram in Fig. 2A demonstrates a series of silk sutures being placed along the mesenteric edge to hold this part of the nipple valve in place. In Fig. 2B the sutures have been tied, intussusception begun. The nipple valve is then completed by placing many sutures around the circumference of it (Fig. 2C). The reservoir is finally closed (Fig. 2C, 2D) and then firmly anchored to the abdominal wall (Fig. 3A). Some of the early groups writing about this procedure did not fix the reservoir to the abdominal wall, so there was a great deal of difficulty intubating the reservoir. In Fig. 3C the reservoir is completed, and an ileostomy catheter is left in the reservoir. The reservoir lies in the pelvis, and exits through the rectus muscle, and unlike a conventional ileostomy, there is no need to have a spout to project into an appliance, and so the stoma is matured flush at skin level. At completion the capacity of the reservoir is approximately 75 cc, and the capacity will grow steadily over the next few months. Its increase is determined by the frequency of emptying. We feel that it is quite important that the capacity increase very slowly, so that the nipple valve can firmly heal before pressure builds up and deintussuscepts the nipple. The high failure rate in many series was the result of intubation being carried on infrequently in the beginning; the reservoir would distend, and the nipple valve would be extruded.

There are very definite contraindications to this procedure. It should never be done as an emergency procedure, or in managing a patient with severe debility. We feel that the procedure has no place in a patient having a subtotal colectomy. It may make excising the rectum,

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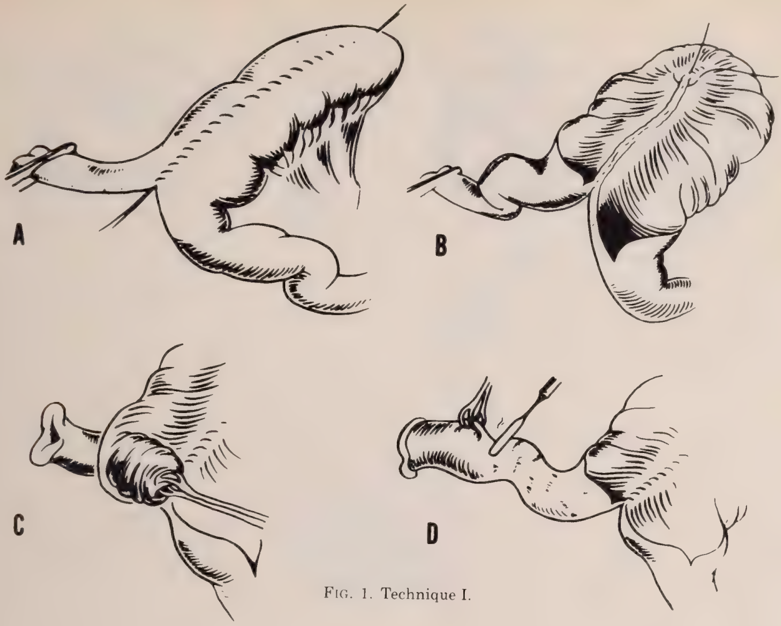

FIG. 1. Technique I.

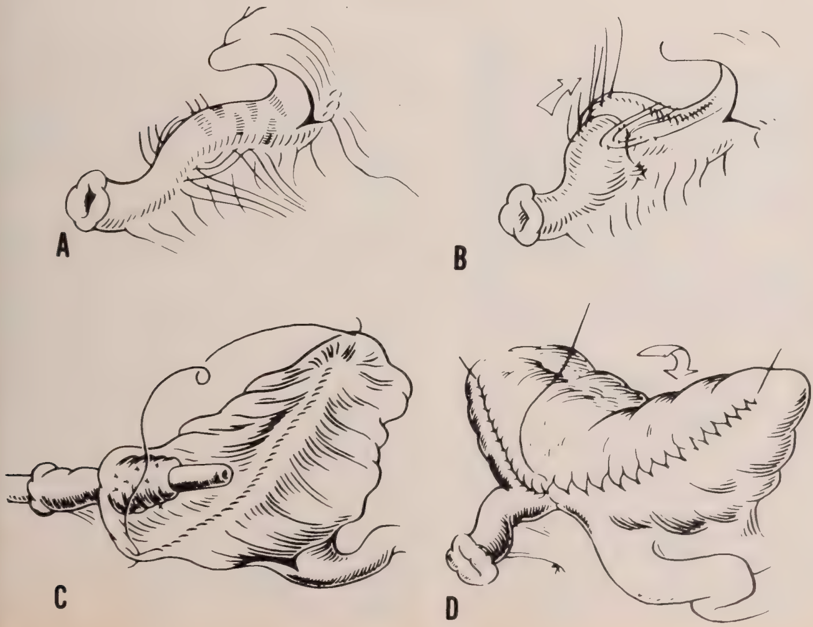

FIG. 2. Technique II.

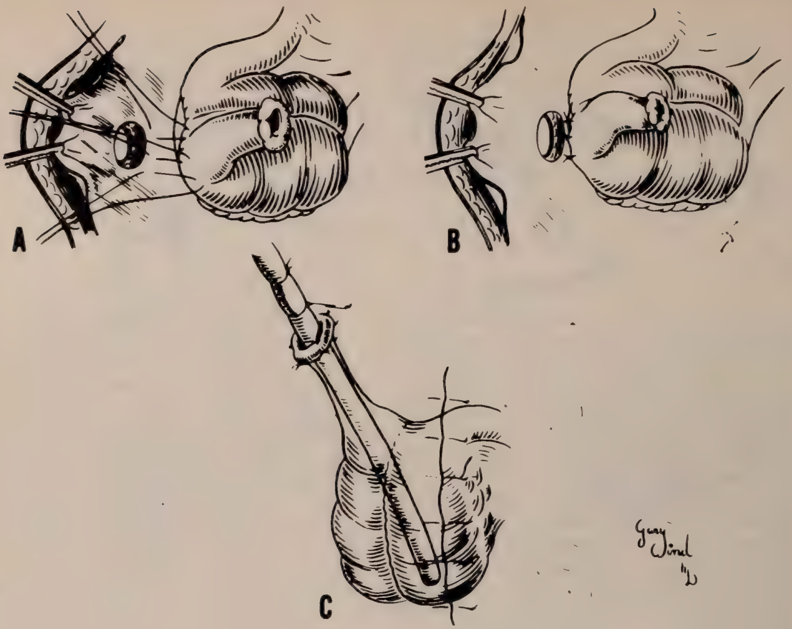

FIG. 3. Technique III.

when this becomes necessary, extremely difficult. It would be much easier, at the time of removal of the rectum, to convert the standard ileostomy to a continent ileostomy. We feel the procedure has no place in Crohn's disease. Recurrence in the reservoir would necessitate sacrificing an extra 40 to 50 cm of small bowel. Of extreme importance is that the procedure has no place in treating the nonreliable patient. We depend on patients to follow a very rigid emptying schedule, early in their postoperative course. We had some difficulties early in our experience with nonreliable patients. Interesting reports in the literature describe patients in psychiatric institutions who have had this procedure, and the disasters that took place. Table I shows the postoperative complications that we have experienced in our first 300 patients with a follow-up of six months to ten years. Fourteen patients have had hemorrhage from the reservoir. Eight of these patients required transfusions. None required surgery. Three patients have had pulmonary emboli, unrelated to a preceding surgical complication. We have had one patient with a perforated gastric ulcer, a patient who had been on large doses of steroids. We have had eight patients with minor fecal fistulas which closed following sump drainage of the reservoir. We have had two patients who required diverting loop ileostomies until the fecal fistula had closed. In our last 100 patients we have had no suture line leak.

Endoscopy of the reservoir years after surgery demonstrates normal-appearing mucosa but there is significant diminution in the rugal fold pattern following surgery. The bacterial count in the reservoir increases, the most significant change being in the number of anaerobes. Bacteroides concentration ends up much higher than in a normal ileostomy. The only problem with studies like this is that they depend very much on how frequently the patient empties the reservoir, and how soon after surgery the colony counts are done. I mention the bacterial studies because a new entity has been described, a condition we have called "pouchitis," a mucosal inflammation of the lining of the reservoir. The frequency of this condition very much depends on how carefully one screens patients for Crohn's disease when accepting them

TABLE I

Postoperative Complications
300 Patients

Complication	No. of Patients	Comment
Minor fecal fistula from ileal reservoir	8	All closed rapidly using sump drainage of the reservoir
Major fecal fistula from ileal reservoir	2	Required temporary diverting loop ileostomy proximal to the reservoir. All leaks sealed
Intestinal obstruction	6	Surgical lysis of adhesions
Hemorrhage from ileal reservoir	14	Minimal in 6; 8 required transfusions. Hemorrhage at time of expected suture line slough (postoperative day 7–12)
Pulmonary Embolus	3	Unrelated to any preceding surgical complication
Perforated gastric ulcer	1	A patient who had surgical lysis of adhesions and was receiving large doses of corticosteroids developed a perforated gastric ulcer requiring plication

for this operation. In our own experience, we have had a number of patients, approximately 10%, who have developed pouchitis. In most, it has been an overgrowth phenomena; it responds rapidly to broad-spectrum antibiotics and frequent irrigations of the reservoir. In several of the patients, the inflammatory process did not disappear very quickly; we think that there may well have been an error in diagnosis and that these patients in fact had recurrent Crohn's disease.

Several of the difficulties one encounters with the nipple valve following surgery are quite easily correctible using an endoscope. These studies were done with Dr. Jerry Waye. An adhesive band between the nipple valve and the wall of the pouch can cause incontinence. Pouch distention would pull the nipple valve open. These adhesive bands are easily severed with cautery. Occasionally during routine endoscopy of the reservoir one sees a small fistula in the nipple valve. When the fistula is very small and lying midway in the valve, there is enough valve above it so that the patient remains continent. Some patients are not quite so fortunate. A fistula at the base of the nipple valve and of large size produces significant incontinence. What is diagnostic is that the patient has no difficulty in intubating the reservoir, and yet is incontinent. Endoscopy is the method of choice in defining the reasons for incontinence. This kind of fistula is fairly easily correctible with a circumstomal incision, lifting the pouch up out of the abdomen and separating the fistulas and closing with two suture lines. Occasionally, however, it has been necessary to turn the pouch around and use the afferent limb for a new stoma and nipple valve. Another cause of incontinence is the complete deintussusception of the nipple valve. If the surgeon has been kind enough to leave enough outflow tract, one can just recreate a nipple valve in the manner that should have been done primarily, and it will be enough. Sometimes there is a very short outflow tract to work with and the afferent limb must be used to create a new nipple valve and outflow tract.

The reason we believe that this procedure has no place in Crohn's disease is the significant number of recurrences. For example, one young patient who had a continent ileostomy for a number of years developed recurrent Crohn's disease in the afferent limb, leading into the reservoir. The reservoir itself, though inflamed, was not as diseased as the limb leading into it. This patient refused excision of the reservoir and therefore just the afferent limb with the diseased segment was excised and reanastomosed into the reservoir.

What kinds of results can be achieved with this procedure, if the patients are chosen carefully? Table II details our experience with our first 300 patients after the initial operation.

TABLE II

Fecal Continence in 300 Patients with Reservoir Ileostomy After Initial Procedure

No. of Patients	Percent	Result
267	89	Continent; appliance never worn
32	11	Occasional incontinence; bag never worn
1	.3	Frequent incontinence; ileostomy bag occasionally worn

TABLE III

Reoperating for Problems with Pouch or Stoma
300 Patients

No. of Patients	Percent	Comment
6	2.0	Skin stricture
30	10.0	Nipple valve revision Incontinence or difficult intubation
3	1.0	Nipple valve revision prolapse
2	.66	Reservoir removed

Eighty-nine percent of the patients are completely continent and never wear an appliance. Eleven percent of the patients are occasionally incontinent, but never wear an appliance. One patient in this series required an ileostomy appliance.

Table III outlines the reasons for reoperation in this group of patients. Two percent of patients had skin strictures. These were easily repaired by local Z-plasties. Ten percent of our patients have required nipple valve revision because of incontinence or difficulty in intubation. We have had three patients who required nipple valve revision because of prolapse. Two patients have had their reservoir removed.

The results of this operation have considerably improved in all of the centers doing large numbers. The reasons for the improved results are that (a) the patients have been keeping their tube in the reservoir for a prolonged period of time before beginning intubation; (b) more attention is being directed to the mesenteric aspect of the nipple valve; and (c) much more damage is being done to the serosa to prevent slippage of the valve. We also feel that the greater effort to fix the reservoir to the abdominal wall has improved results. Of great importance is choosing patients who will be compliant and follow instructions.

We feel that the continent ileostomy can be performed with very acceptable results. The patients are less depressed than after standard ostomy surgery and are being sent for surgery earlier in the course of their illness.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

The Problem of Postoperative Recurrence

ADRIAN GREENSTEIN, M.D.

Although Dalziel (1) first described the major features of Crohn's disease in 1913, it was not until the classic paper by Crohn, Ginzburg, and Oppenheimer (2) in 1932 that knowledge about the disease became widely disseminated. At that time Crohn hoped that resection would lead to cure; however, he did observe that recurrent disease developed in two patients: in one, proximal to an ileotransverseostomy following resection, and in the other, proximal to the loop of the anastomosis following a side-to-side ileotransverse colostomy. During the following three decades it became obvious that recurrent disease was a common sequel to operation for Crohn's disease of the small bowel and for ileocolitis. This entity was recognized in 1934 by Colp (3), who described a case of nonspecific granuloma of the terminal ileum and cecum.

In 1951 Drs. Garlock and Crohn et al (4) at The Mount Sinai Hospital reported a higher recurrence rate following resection than following bypass. However, many of the earliest cases had been resections, and thus the follow-up on these patients was longer. It is now well established that recurrences are greater following bypass with residual disease than following resection of all overtly diseased portions. In order to achieve a cure, larger and larger segments of normal bowel were removed and by 1952 Colp and Dreiling (5) suggested that 60 cm of bowel proximal to the diseased segment be removed. At the present time Scandinavian authors still favor radical resection, noting lower recurrence rates after more extensive resection of the small bowel (6), but most other surgeons remove only 5 to 10 cm of normal-appearing bowel.

Numerous factors have been noted to be associated with differences in postoperative recurrence rates and have been said to influence postoperative recurrence. These factors include age at onset of disease, ethnic group, anatomic localization of disease, preoperative duration of disease, type of operation performed, length of bowel resected, and microscopic disease at the resection margin, as well as the type of pathology found. High postoperative recurrence rates have been found following small-bowel resection (7-9). The question of recurrence rates following disease confined to the large bowel, however, remains controversial (10–12).

Diagnosis of Recurrent Crohn's Disease

The diagnosis of recurrent Crohn's disease is established by a characteristic small-bowel series with spot films of the terminal ileum demonstrating skipped areas, loss of normal mucosal pattern, eccentric narrowing of the bowel, fissures, fistulae, and collar-button ulcers. Barium enema similarly confirms the presence of disease above or below the anastomosis, and endoscopy confirms the presence of Crohn's disease and possibly even reveals granulomata if an adequate biopsy is taken.

Definition of Recurrent Disease

In 1967 Lennard-Jones and Stalder (9) divided recurrences into three types: (a) recurrence of clinical symptoms without evidence of new disease; (b) recurrent symptoms with radiologic and/or histologic proof of disease; (c) recurrent disease requiring further surgery. The first definition of recurrence encourages overestimates because after resection of the distal ileum many patients develop symptoms such as choleretic diarrhea due to the irritant effect of bile salts upon the colon. The last definition encourages underestimates, because many persons with active recurrent disease are treated quite adequately by medical means and may not need surgery for many years. The second definition is the most accurate and should be used whenever possible. In 1965 Atwell et al

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(13) and in 1971 deDombal et al (8) noted that in many instances residual disease was left in situ at the time of surgery. They observed that this residual disease should be differentiated from true recurrent disease and, should symptoms recur, should be categorized as recrudescent rather than recurrent.

Methods of Calculating Recurrence Rates

Estimation in Crohn's Disease. In the earliest papers on Crohn's disease, recurrence rates were estimated in a crude fashion: noting the number of recurrences and dividing this by the total number of patients studied. This did not allow for varying periods of follow-up and in 1967 Lennard-Jones and Stalder (9) utilized actuarial methods incorporating the data obtained in an actuarial table. Actuarial methods were used by Greenstein in 1975 (14), and in 1976 Truelove and Pena (15) drew up survival curves using a similar type of analysis. In 1982 Sachar et al (16) took this form of analysis one step further, utilizing multivariate analysis to evaluate the independent influence of different factors upon recurrence.

Crude Rates. Crude recurrence rates have been estimated by various authors for different anatomic localizations of disease and different operative procedures. In 1954 Van Patter (17) found a recurrence rate of 63%, leading to a rather gloomy estimate of the ultimate recurrence rate. Atwell et al (13) in 1965 found recurrence rates of 58% for ileitis, 46% for ileocolitis, and 57% for colitis. Recurrence rates for bypass incontinuity in ileitis ranged between 61% and 92% (7, 13, 18, 19) and for bypass with exclusion from 60% to 75% (14, 20, 21). However, in 1958 Colp and Dreiling (5) reported a 29% recurrence rate for bypass. In ileocolitis, bypass incontinuity rates as high as 100% (20) have been recorded, whereas with exclusion bypass rates range from 60 to 75% (14). In ileocolitis recurrence rates following resection with anastomosis range from 12 to 71% (8, 22–25). In the presence of associated ileostomy for ileocolitis, recurrence rates vary between 11% (8) and 52% (23). In granulomatous colitis following resection with anastomosis with rectal sparing, rates have ranged from 12% to 100% (8, 22, 23, 26). For proctocolectomy with ileostomy the figures range from 0% to 45% (12, 27–30).

Actuarially Calculated Rates. In 1967 Lennard-Jones et al (9) found a 23% recurrence rate at five years, and a 52% rate at ten years. All authors using these methods have found a steady increase in recurrence with time. Five-year recurrences have ranged from 19% to 43%, and fifteen-year recurrences from 23% to 86% (7, 8, 14, 31–34).

Multivariate Analysis. Sachar et al (16) have recently studied recurrence rates using multiple combinations of associated factors by the method of multivariate analysis. They have noted that although many factors are associated with recurrence, certain factors determine or are more closely related to such recurrences. In particular they have noted no difference between granuloma positive and negative cases, a considerable difference between ileitis, ileocolitis, and pure Crohn's colitis patients, and an important influence of preoperative duration of disease on rates of postoperative recurrence.

Factors Affecting Recurrence Rates

Age. Most papers have shown an association of age with recurrence rates. Van Patter (17) found a 65% recurrence rate below the age of 50 and a 22% recurrence rate above that age. Stahlgren and Ferguson (35) found 62% below age 30 and 39% above age 40. A similar association of age and recurrence was noted by Trevor Cooke in 1980 (36) and Goligher in 1979 (30). Calculating by actuarial methods, Greenstein (14), Cooke (36), Steinberg (32), and Sachar (16) all found higher recurrence rates, both actual and cumulative, in patients who were younger at the onset of disease.

Sex. Although most authors have found no difference in recurrence rates between men and women (16, 35), a worse prognosis in women has been reported by deDombal (8), Truelove and Pena (15), and Weterman (37), particularly with regard to survival. Kyle (38) found a higher recurrence rate in young female patients with short duration of disease prior to surgery. However, Sachar et al (16) recently found no difference among 51 male and 51 female patients when their recurrence rates were calculated actuarially.

Anatomic Site of Disease. There is little question about the high recurrence rates following resection for small-bowel disease when the Crohn's disease is limited to the distal ileum. Recurrence rates range from 42% to 86% at 15 years (8, 14, 16, 33, 39). In regard to Crohn's colitis, however, there is considerable debate on true recurrence rates. This applies to total colectomy and ileostomy and not to colon resection with ileorectal anastomosis. Following ileorectal anastomosis, recurrence rates range from as high as 55% at five years (33) to 75% overall (40). These figures are comparable with the 86% recurrence rates reported by Greenstein et al (14) from The Mount Sinai Hospital for what were largely resection with reconstruction or bypass procedures in a series of patients with a somewhat lower overall onset age than most other series.

Reports on Crohn's colitis emanating from Boston in the 1970s suggested that recurrence rates following total proctocolectomy and ileostomy were as low as 0% to 3% (27, 28). Since 1967, Glotzer has noted a steadily increasing rate of recurrence, reaching 16% by 1980 (10). Others from London and Leeds report incidences ranging from 6.2% (London) (24) to 14.7% (Leeds) (30). Recently Hellers (33) reported 25% recurrence after five years and 40% recurrence after 10 years following total proctocolectomy and ileostomy. This is somewhat lower than for small-bowel disease, but quite considerable compared with many other series, and comparable with the 45% reported by Korelitz et al from New York City (12). Despite the controversy in this area, it seems that more and more groups are reporting a considerable recurrence rate even following total proctocolectomy and ileostomy for Crohn's colitis or ileocolitis, if true actuarial studies are carried out with a long period of followup.

Anatomic Site of Recurrence. Most recurrences occur in the neoterminal ileum just above the anastomotic line. A recent study of patients with ileocolitis by Koch et al (41) showed proximal recurrence in 19%, distal recurrence in 19%, and both proximal and distal recurrence in 62%; among patients with regional enteritis, 70% developed proximal recurrence but only 30% developed proximal and distal recurrence, and no patient developed distal recurrence alone. Korelitz (42) found that among patients with ileocolitis, 39% developed distal recurrence, 35% proximal recurrence, 16% proximal plus distal recurrence; only 14% developed no recurrence. If one makes allowance for the patients with no recurrence in this series of 61 patients, the percentages are comparable with those found by Koch (41), except for the lower percentage of simultaneous proximal and distal recurrences in the Korelitz series.

Preoperative Duration of Disease. Van Patter in 1954 (17) was the first to examine the relationship of preoperative duration of disease to recurrence, noting increased recurrence rate with increased duration. However, deDombal in 1971 (8) noted the highest rates with the shortest preoperative duration of disease. In two recent studies (16, 43), shorter preoperative duration of disease was associated with high recurrence rates when examined by both simple and actuarial methods.

Reoperation. Despite the early reports of Garlock et al (4), more recent studies comparing actuarially derived recurrence rates following bypass and resection have clearly demonstrated that bypass, for both residual and recurrent disease, has a considerably greater reoperation rate, particularly in the earlier years following primary surgery (7, 14).

The number of reoperations following each succeeding operation is a subject which is somewhat controversial. Greenstein in 1975 confirmed what Lennard-Jones (9) had noted in 1967—an increased rate of reoperation after the second operative procedure. He also noted, however, with small numbers of patients a tendency to further increases after the third and fourth reoperation. This tendency could not be substantiated statistically. Hellers (33) has recently noted a higher reoperation rate after the second operative procedure both for his overall series, and following ileocecal resection and ileocolic anastomosis. However, Trevor Cooke from Birmingham (36) has followed a large series of patients for 25 years and finds no difference in the reoperation rates following from one to five operations.

Radical vs Conservative Resection. There is considerable variation in the amount of normal bowel resected proximal to the diseased segment. Although Dr. Crohn advised resection of 60 cm (5), most authors now take between 5 cm and 10 cm of normal bowel, attempting to preserve as much bowel as possible. However, Swedish authors (6, 44, 45) recommend greater resections varying from 10 to 35 cm, believing that a more radical resection will result in a lower recurrence rate. Recent studies by Pennington et al at Johns Hopkins (34) and Lee at Oxford (46) have found no difference in recurrence rates if there is macroscopic or microscopic disease at the resection margin. Several authors have noticed an increased risk of recurrence with extensive involvement of bowel (13, 17, 18, 47). Van Patter et al (17) found that the difference only became apparent if more than 80 cm was diseased.

Other Factors. There is considerable disagreement about the value of frozen section at the time of surgery. Few authors now find this to be of great value, although some of the

Scandinavian surgeons, such as Karesen (6) still utilize the technique. Lymph-node involvement and resection of large numbers of lymph nodes has been advocated as important in reducing recurrence rates, but it is generally agreed today that there is no point in removing excessively large numbers of lymph nodes because of potential damage to the bowel if major blood vessels are compromised. There is a dispute about the importance of granulomas and recurrence. Some authors, for example Chambers and Morson (48), have found that granulomas appear to exert a protective effect, but Sachar et al (16) and Pennington et al (34) have disputed this.

Quality of Life Following Surgery

The question of recurrence rates in Crohn's disease is a much debated one but the major factors related to recurrences are gradually being more clearly defined. All major recent series agree that surgery is of great value in controlling the symptoms of the disease, and most authors find that patients are extremely satisfied with the operative procedure and are relatively symptom-free in the interoperative period (21, 49).

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Animal Transmission Models

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We have been reminded by Dr. Ginzburg that attempts to unravel the etiology of ileitis and colitis by animal transmission work date back nearly fifty years. I also recall that in the 1960s Dr. Gelernt, before he was putting pouches into people, was trying to put ileitis into rabbits, without a good deal of success. But it is primarily in the last ten years or so that popular enthusiasm for animal transmission has been rekindled by the observation in London by Mitchell and Rees that they could successfully apply a technique they had used for cultivating the leprosy bacillus in the footpads of mice. Applying that techniqe to the study of Crohn's disease, they took intestinal and lymph node homogenates from one patient with Crohn's disease and injected it into a large number of mice. Mitchell and Rees found that over the next 6 to 24 months some of these mice gradually developed granulomas in their footpads at the site of injection. Their observations were reported in *Lancet* just about ten years ago. Soon thereafter, the assault on the problem of animal transmission threatened to depopulate the world's supply of mice and rabbits by using them all up in Crohn's disease transmission experiments.

The First Phases: 1970–1978

These experiments went through several phases, not necessarily chronologically, but at least intellectually. In the first phase there were three steps. It was demonstrated, first, that crude or coarsely filtered homogenates of Crohn's disease tissue produced granulomas in the mouse footpads. This work was reproduced a few times. Next, it developed that crude or coarsely filtered homogenates of Crohn's disease tissues produced granulomas when injected into the ileum of rabbits. Third, it turned out that granulomas were elicited not only by crude or coarsely filtered homogenates but also by fine filtrates of 0.2 microns. This last finding meant that intact cells or conventional bacteria were effectively ruled out as a granuloma-producing agent, still leaving viruses or atypical bacteria or macromolecules as candidate agents for this phenomenon.

This work was all done in the early and mid-1970s, and it all emanated from three laboratories: Mitchell and Rees and Cave in London, Donnelly in Dublin, and Dr. Robert Taub and I and our colleagues here in New York. Our technique was simple. A piece of bowel, or a lymph node, would be taken at surgery from a Crohn's disease patient, or more importantly, from a control patient. The tissue was then homogenized, suspended 13% to 15% in medium, and injected through the dorsum of the foot into the footpads of the mice. Then the footpads would be biopsied at 35, 150, and 225 days. Granulomas were certainly produced by this technique. These granulomas could actually erode right through bone. Moreover you could inoculate these mice with these homogenates just about anywhere and produce a granuloma, even in the ears.

The next phase in the unfolding of the granuloma transmission story was a report that these granulomas would not only appear at the site of injection, but would be disseminated throughout the animal. Homogenates injected intravenously would reportedly home in and produce granulomas in the bowel and other tissues. Homogenates injected into the footpads, when the animals were sacrificed, were said to have led to the development of granulomas in the ileum of these mice. These reports emanated only from the London laboratory. We, and others, were never able to reproduce these phenomena when we sacrificed our mice and studied their spleens, lungs, livers, lymph nodes, and other organs. We could never find granulomas disseminated anywhere beyond the site of injection.

The next phase was that serial passage of

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granulomas was reported. Footpad homogenates could be transferred from one mouse to another, repeatedly producing new granulomas, up to at least four passages. Similarly, when ileal granulomas were produced by Crohn's disease homogenates in rabbits, those granulomatous lesions could also be passed from rabbit to rabbit. These reports also came exclusively from the same London laboratory. We were not able to reproduce that passage phenomenon with Crohn's disease in mice. In one instance we achieved a single mouse-to-mouse passage of a granuloma induced by a sarcoid lymph node homogenate, but we were never able to produce passage from animal to animal with Crohn's disease homogenates.

So by the end of 1978, we still had only straws in the wind, but no confirmed proof of a replicating transmissable agent. What we did have, though, by the end of 1978 were a lot of headaches, a lot of problems that we couldn't sort out. In an editorial that we wrote in *Gastroenterology* that year (1), we summarized these problems into four categories. The first category that we discussed was *reproducibility*. For example, efforts were made to reproduce the granuloma transmission phenomenon by a group of meticulous workers in Cardiff, who tried to transmit granulomas from Crohn's disease patients into mice, rats, rabbits, and guinea pigs. They took granuloma-bearing tissues from 24 patients with Crohn's disease, and injected homogenates into footpads, intestines, and eyelids of over 400 normal and immunodeficient mice, rats, rabbits, and guinea pigs. They followed the animals up to a year and a half, examined over 2000 histological sections, and never found one single granuloma. More recently, workers in Scandinavia tried to reproduce granuloma transmission in both conventional and germ-free animals, and they were not able to transmit granulomas either.

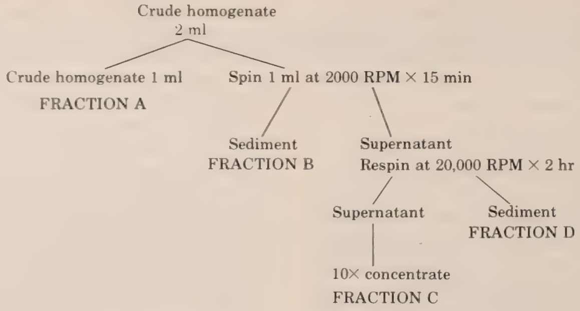
A second problem that we described was *uniformity*. Every laboratory was using a different methodology. Each laboratory was finding different results in terms of the anatomic distribution and the time course of development of the lesions. Each laboratory also had differing interpretations of what constituted a granuloma. Some things that to the eye of one beholder were granulomas, in the eyes of other beholders were just nonspecific aggregates of histiocytes.

A third problem besides reproducibility and uniformity was the problem of *specificity*. What about the controls? Everybody who had reported granuloma transmission in Crohn's disease agreed that it also happened in ulcerative colitis. Now, that's no problem if you adopt a unitary hypothesis of these diseases. But the real problem was that granuloma transmission also occurred in noninflammatory bowel disease controls. Donnelly in Dublin found that when rabbits were inoculated in the ileum with Crohn's disease homogenates, 21% of the rabbits developed local intestinal granulomas. When they were inoculated with control tissue, 58% of rabbits got granulomas. We also encountered a similar problem with specificity. Dr. Taub, Dr. Janowitz, and I and our colleagues found that while we were regularly getting granuloma transmission from Crohn's disease, in four out of nine cases we also found granulomas in the footpads of mice inoculated with control tissue: normal colons taken from patients with familial polyposis, one normal colon distant from a resection margin for carcinoma of the rectum, and one inflamed colon that had been used as part of an esophageal interposition operation.

So, we had problems with reproducibility, uniformity, specificity, and finally, with *pathogenetic interpretability*. In other words, what did these lesions mean anyhow? There were at least four issues that were raised by the question of interpretability. First of all, a granuloma isn't the same thing as Crohn's disease. Dr. Cave's rabbits developed intestinal lesions with granulomas that, indeed, did look like human Crohn's tissues; but using identical techniques in Chicago, Simonowitz and his colleagues in Dr. Kirsner's group found only peculiar, but rather nonspecific inflammation in the inoculated rabbit intestines without any convincing resemblance to human Crohn's disease. Second, it was hard to interpret the pathogenetic significance of these findings because when the assay of granuloma transmission was sensitive and easy to produce it was highly nonspecific. It turned up a lot in controls. When techniques were used with various filtrations, to try to make the lesions more specific and occur only in inflammatory bowel disease, the assay then became extremely insensitive, occurring in only 5% to 7% of animals. Moreover, sometimes the pattern of granuloma transmission simply did not make sense. Drs. Cave, Mitchell, and Rees, for example, described animals in whom intraperitoneal and intravenous inoculations produced granulomas in the footpads. Then, finally, the issue had to be addressed as to whether the granuloma transmission phenom-

TABLE I

Fractionation Protocol for Granuloma Production



enon had anything to do with what other people were reporting as candidate agents, namely viruslike particles, that Dr. Dourmashkin discusses in more detail.

Step 1: Origin of Granulomas and Viral Particles

In the late 1970s there were three steps that were taken to resolve some of these problems. The first step was taken here at Mount Sinai, where we launched studies to try to figure out where the granulomas were coming from and whether they had anything to do with some of the viral particles that were being described. I want to show some of our data from those experiments that have not been previously published.

We attempted to fractionate homogenates from Crohn's disease and control patients to try to determine which fractions of these homogenates were producing the granuloma transmission phenomenon, and whether they could correlate with a fraction in which a virus might travel, or a fraction in which a macromolecule might travel, or a fraction in which "junk" might turn up. The fractionation protocol is shown in Table I. We used two ileitis homogenates and two controls from normal colons far away from the margins of cancer. The results appear in Table II. The only fraction that consistently gave us granulomas was fraction B, a "junk fraction," being the sediment from the low-speed spin of the crude homogenates. This fraction produced granulomas from all four tissues, the two Crohn's disease specimens and both controls.

The next step, then, was to try to see whether the fractions that transmitted granulomas were the same fractions that yielded another observation we had made in some of these homogenates, namely the presence of 30-nanometer particles that looked a bit like viral particles. The slightly more elaborate fractionation protocol for these experiments appears in Table III. If there were indeed viral particles, we might have expected to find them in fraction F, the ultrafine filtrate of the high-speed supernatant. But it turned out that there were peculiar nonspecific particles in all of the fractions, and none of them agglutinated with autologous

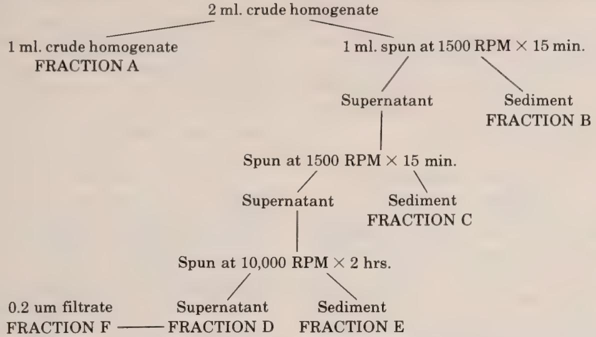
TABLE II

Granuloma Production by Fractions of Tissue Homogenates

Fraction	Ileitis	Ileitis	Control*	Control*
A	Neg.	Granulomas	Neg.	Fibroblastic reaction ± granuloma
B	Granulomas	Granulomas	Granulomas	Granulomas
C	Neg.	Fibroplastic Reaction	Neg.	Nonspecific Inflammation
D	Neg.	Neg.	Neg.	Neg.

* Normal colon from cancer resection.

TABLE III
Fractionation Protocol for Electron Microscopy



serum. So those particles were not behaving the way that viruses should, and I know that Dr. Dourmashkin will want to say more about so-called virus particles in the next presentation.

What we had determined at this point, then, was that the granulomas in our assay system appeared probably to be a nonspecific reaction to the heaviest particulate matter in the homogenates from ileitis and control patients alike. There was no evidence that any of the 30-nanometer particles we had seen in patients' tissues were viral. They didn't correlate with the fraction that gave granuloma production, they were not specific for Crohn's disease, and they didn't agglutinate. That was the first of the three steps I alluded to in an effort to resolve some of the problems in granuloma transmission work.

Step 2: Interdisciplinary Workshop

The second step was taken at the end of 1978, when the American Gastroenterological Association and the National Foundation for Ileitis and Colitis jointly sponsored an interdisciplinary workshop in Tarrytown, New York, bringing in experts in the fields of virology, biochemistry, immunochemistry, and so on, to try to achieve some sort of consensus (2). The workshop panel on animal transmission, with blinded review by expert reviewers, came to several important conclusions: (a) In the published studies, some of the granulomas that had been reported were not granulomas, but were spontaneous murine neoplasms. (b) Some of the granulomas that had been reported as occurring at the site of Crohn's disease injection were actually foreign body granulomas associated with fragments of hair and bone in the footpad. (c) Other granulomas were associated not with hair and bone, but with some peculiar foamy foreign body material that has never been identified. The conclusion of the panel, understandably, was that there was no evidence as yet for a replicating transmissable agent in Crohn's disease.

Step 3: Uniform Protocols

The third step was also launched in the late 1970s. It was a collaborative national inflammatory bowel disease research group coordinated by Dr. Gary Gitnick of UCLA, which received some seed funding from the Ileitis and Colitis Foundation and a subsequent grant from the NIH. The aim of this cooperative effort was to adopt uniform protocols and to exchange materials among our various laboratories so that we could at least eliminate some of the questions of reproducibility, uniformity, and specificity. This effort failed to reproduce granuloma transmission in rabbits, even in Dr. Cave's laboratory in Chicago, where it had originally been described.

Now, does all this mean that animal transmission experiments are a complete waste of time? Our group came very close to saying so in 1975 when we made our presentation at the Seventh International Symposium on Sarcoidosis and Other Granulomatous Diseases. Dr. Taub said that "although these data allow the hypothecation of infectious or autoantigenic transmissable agent, further support for such a hypothesis must come from isolation and characterization of the agent itself, and demonstration of its specificity. An important alternative explanation for all these data, is that injected disease homogenates retain lymphokines, mediators of inflammation, and macrophage attractants of the parent tissue, which may evoke mouse lesions that are irrelevant to the etiology of antecedent human disorders" (3).

Potentials of Animal Transmission Studies

But before we close the book completely on animal transmission, I want to make one final point. The animal transmission system is not merely a cultivation technique to try to grow a microorganism. It also has the potential of revealing some interesting immunopathologic phenomena. I want to give just two examples of that potential. First, in Dr. Taub's work here in the mid-1970s, we used a syngeneic transfer assay to try to study the effects of these tissue inoculations on T cell stimulation or T cell depletion in the recipient mice. Using a crude assay of that time, we took cells from popliteal lymph nodes draining the areas of footpad inoculation, pooled them, labeled them in vitro with chromium-50 sodium chromate, injected them into syngeneic mice, and saw where these radioactively labeled cells homed to. It had previously been demonstrated that this was one measure of T cell depletion versus stimulation in donor animals. While the spleen and liver homing cells were unchanged between control sarcoid and ileitis homogenates, there was a slight but significant increase in the homing of these cells to peripheral nodes and to mesenteric nodes. This meant at least that there did not appear to be a massive T cell depletion of the recipient animal.

More recently, Dr. Das, from the Albert Einstein College of Medicine, has utilized animal transmission techniques to inoculate athymic nude mice with Crohn's disease homogenates, to produce lymphomas in them, to passage the lymphomas into other mice, and then to identify by immunofluorescent techniques an antigen in the mouse lymphoma cells that reacts specifically with antibody in the sera from Crohn's disease patients only. This work has not yet been corroborated, but it is undergoing confirmatory testing now in Dr. Das's laboratories, in collaboration with our institution and with Dr. Singleton and Dr. Kern's institution in Denver, as well as with the cooperation of the New York Chapter of the National Foundation for Ileitis and Colitis, under the supervision of Dr. Peter Holt.

In conclusion: while animal transmission studies have most certainly not yielded any specific etiologic agent, they have reflected the inextricable interplay of both microbiologic and immunologic factors in the development of inflammatory bowel disease. Each of these areas is more fully discussed by Dr. Dourmashkin, looking at the microbiologic factors, and Dr. Heimann looking at the immunologic factors.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Microbiologic Approaches

ROBERT R. DOURMASHKIN, M.D.

In 1932 Crohn and his associates attempted but were unable to isolate a tubercle bacillus from the affected intestine or mesenteric glands of patients with regional ileitis, either by inoculation of guinea pigs, rabbits, or chickens, or by in vitro culture. Since then, the theory of a microbial etiology for Crohn's disease has persistently seemed likely, but no definite proof has been forthcoming. To explain the distinguishing characteristics of the organisms we have studied, I have prepared a few simple figures.

Fig. 1 is a picture of the pneumococcus stained in such a way that you don't see the capsule. Around the edge of the organism is the cell wall, which consists of a layer of phospholipid; right inside that outside layer is a layer of teichoic acid, and underneath is the cell membrane which you can't see at this magnification. L-forms, named after the Lister Institute, are bacteria which have lost this external cell wall and just have their external membrane, which enables them to pass through bacterial filters. Fig. 2 illustrates the class of organisms called *Mycoplasma*. They are free-living and are banded by a 75-Angstrom external membrane consisting of phospholipid, and have internal components of RNA and DNA. Fig. 3 is a photograph of *Chlamydia* budding inside a vesicle in the cell. They are also not dependent on cellular mechanism for their replication, but they do exist inside cells. They multiply by binary division and neither *Mycoplasma* nor *Chlamydia* are ever seen to bud from cell membranes.

The viruses, on the other hand, are entirely dependent on cellular mechanisms for their replication. The results of the various studies on the microbial etiology of Crohn's disease are worth exploring in some detail. With regard to the tubercle bacillus that we've looked at since the time of Dr. Crohn in 1932: Jones, Lennard-Jones, and Lockhart-Mummery (1) found in 1966 that Crohn's disease did not respond to antituberculous therapy, supporting Crohn's original view. However, the possibility of *Mycobacterium* being involved was raised again. *M kansasii* was reportedly isolated in one case by Burnham, Lennard-Jones, and others (12). This work was not reproduced. These workers also isolated a cell wall variant organism in their cultures. In addition, increased sensitivity to antigens derived from mycobacteria was found by these and other observers. In 1965 Crohn found that acute ileitis caused by *Yersinia enterocolitica* could progress to chronic disease. However, later it was shown that those cases of acute ileitis that were negative for *Yersinia* probably represent an acute form of Crohn's disease, and those that are positive for *Yersinia* do not progress to chronic disease (3). It is likely that *Yersinia* is not related to Crohn's disease. *Campylobacter* can cause an acute colitis that resembles ulcerative colitis. This organism deserves study as to its relationship to chronic disease. Aluwihare (4), in an electron-microscope study of Crohn's disease, found intramural bacteria that could be L-forms. Although other electron-microscope observers did not confirm this finding, Orr and his coworkers (5) succeeded in inducing granulomas in the terminal ileum of rabbits inoculated with L-forms of *Streptococcus fecalis*. Subsequently, Parent and Mitchell (6) succeeded in isolating L-forms of *Pseudomonas,* Group VA, from the intestinal lymph nodes of several cases of Crohn's disease, but not from the intestine of patients with ulcerative colitis or other gastrointestinal diseases.

However, recent work using a highly specific DNA probe for *Pseudomonas* failed to reveal this organism's genome in Crohn's disease tissue. Belsheim and others (7) in Canada, on

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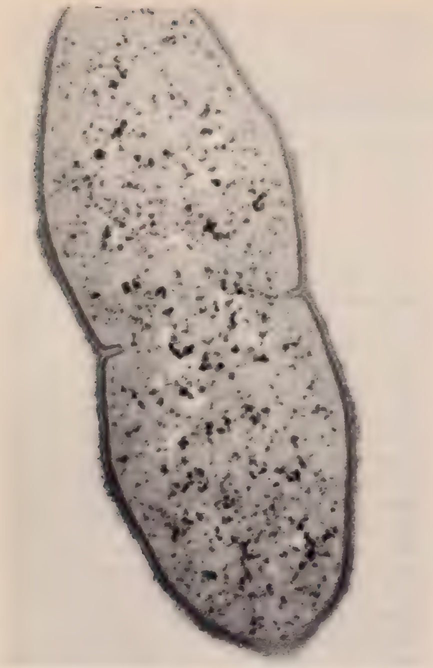

FIG. 1. Electron micrograph of section of pneumococcus, illustrating the cell wall. Magnification, 42,350×.

the other hand, isolated the L-forms of a number of different bacteria in both Crohn's disease and ulcerative colitis, and concluded that the gut environment in IBD is favorable for the growth of these organisms, but made no comment on their etiological nature.

Shorter and his coworkers suggested that a transient enteric infection of varying etiology could initiate autoimmune phenomena. *Chlamydia* have been implicated by serologic data, but other sources have contradicted this finding. Taylor-Robinson in London is currently studying the possibility that anaerobic *Mycoplasma* may be involved in Crohn's disease.

The possibility that a virus may be the cause of Crohn's disease was particularly exciting as a result of the reports of transmission of filtrates in animals. A number of isolations have been claimed which I briefly summarize here. Early attempts at virus isolation and serologic studies by Syverton (8) and by Schneierson (9) were negative for human viruses. Farmer and his coworkers (10) isolated cytomegalic virus from a number of patients with IBD. Later observers questioned the significance of this observation; in other words, it was found, but not considered to be connected with etiology. In 1975 Aronson, Phillips, Beeken, and Forsyth (11) claimed the isolation of a picornaviruslike organism from both IBD patients and patients with other gastrointestinal diseases. Subsequently, members of this group, including Whorwell, reported a more specific isolation of a virus similar to calf rotavirus. However, Kapikian and others (12) at the National Institutes of Health could not find rotavirus in this preparation, but rather demonstrated the presence of contaminating *Mycoplasma* in these isolates. In addition, Gitnick and his collaborators (13) claimed the isolation from IBD of a 60-nanometer-sized agent that caused CPE in a number of cell lines of human, rabbit, duck, and chick origin and reported the passage of the agent in cultures up to 15 times. This agent has recently been demonstrated to behave as a toxin by McLaren (14). Roche and others (15) have failed to identify adenovirus genome in IBD using a DNA probe. Aside from a claim by Reimann (16) to have demonstrated virus particles in Crohn's disease tissue by electron microscopy, most observers have not found any in this way. Separate studies were carried out by Dvorak (17), Tytgat (18), and Phillpots (19). In 1980 I reported the presence of particles budding from microvilli in Crohn's disease (20). However, I doubted whether these represented a virus infection. Fig. 4 shows particles budding from the surface of a columnar epithelial cell in the intestine of a patient with Crohn's disease, showing particles similar to the ends of microvilli, but differing in that they have a very dense core and they budded free from the surface of the epithelium. I said at the time that I did not consider these to be virus particles connected with the disease. However, very recently Lewis et al (21) have made similar, possibly more significant observations in children with Crohn's disease and are continuing their investigations.

A comprehensive report was given by Phillpotts and his coworkers (19) concerning the search for viral agents in Crohn's disease, using a number of techniques involving long-term cultures, lectin binding, interferon production, electron microscopy, reverse transcriptase assay and immunofluorescence with Crohn's disease serum. These workers failed to isolate a viral

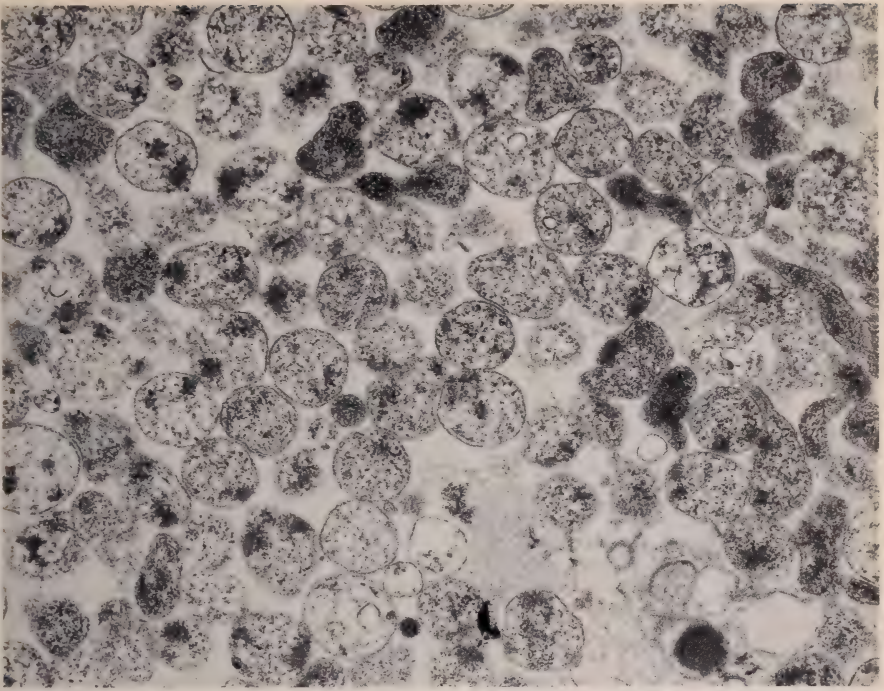

FIG. 2. Electron micrograph of section of mycoplasma from a genital infection. There is a thin-layered cell membrane, in contrast with the cell wall of the pneumococcus. Magnification, 40,250×.

agent in Crohn's disease. However, the authors emphasized that the failure did not rule out the possibility of a viral etiology.

To summarize the evidence that we have presented, here is a classification of microorganisms that have been studied so far: bacteria—*Mycobacterium, Yersinia, Campylobacter,* and *Pseudomonas* L-forms; there are a number of others I have not mentioned. *Mycoplasma* and *Chlamydia* are claimed to be involved. Among viruses there are adenovirus, cytomegalic virus, picornavirus, reovirus, and rotavirus. In other words, a whole host of organisms have all been studied and there has been no definite evidence so far that any of them are involved in the etiology.

It is possible that multifactorial agents play a secondary role in the etiology of the disease. However, there are hints recently that suggest that perhaps we are on the right track after all in our research. One is the growing impression that the autoimmune phenomena and depressed delayed hypersensitivity in inflammatory bowel disease are not related to the primary cause. Another is the fact that the viruses of human diarrhea are unique in that they cannot be grown in tissue culture under ordinary conditions, or passage into animals (22). If there is a virus in Crohn's disease that behaves similarly to the diarrheal viruses, then all our previous efforts at virus isolations have been pointless. For this reason, we have chosen to use human intestinal organ culture to replicate a possible virus in Crohn's disease. These fetal organ cultures will survive almost indefinitely and we have kept them going for two months in our laboratory. Fig. 5 is a picture of a fetal organ culture with growing epithelium and a brush border. These organ cultures are infected with either homogenates of Crohn's disease tissue or cocultivated with Crohn's disease epithelium organ cultures which last for a period of time,

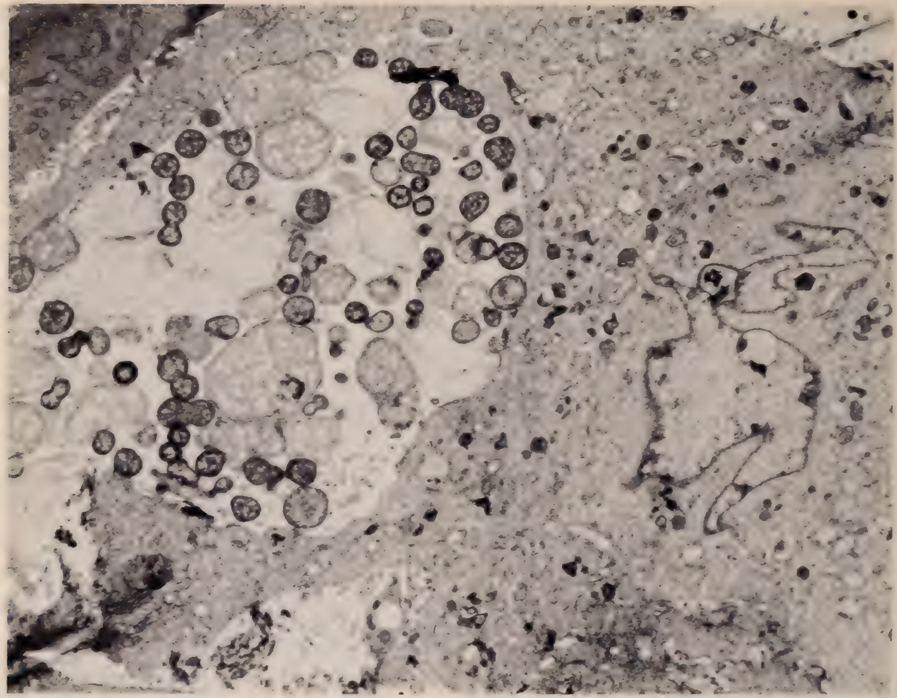

FIG. 3. Electron micrograph of a section of McCoy cell line infected with chlamydia. The organisms are dividing within a cell vacuole. Magnification, 6,860×.

but not as long as the fetal organ cultures. It is too early to assess the results of this work, but what we have found is that infection of human fetal organ cultures with human rotavirus results in the successful replication of the virus in the epithelial layer.

Fig. 6 is a symmetrical array of virus particles growing in the epithelial cells of a human fetal organ culture: round forms, tubular forms, and forms which have an external membrane. However, for reasons that I discuss below, the virus infection cannot be transmitted further than the first passage. A quiet revolution in the study of the diarrheal viruses has recently taken place. First, workers in Japan (22) and then the United States have been able to passage human diarrheal viruses in certain cell lines. All workers agree that the common factors are the elimination of fetal calf serum from the culture medium and rolling of the cultures during incubation. We shall take advantage of these new developments to make renewed efforts at isolating viruses in Crohn's disease, utilizing cell lines in this way and also using human fetal organ cultures. I am happy to report that they survive well without serum in the media.

There is another issue that is important: the pathogenesis of Crohn's disease. Most observers have felt that inflammation and granulomas arise from the submucosa, secondarily erupting into the lumen and causing ulcerations. In my laboratory in England we have data to suggest that the primary insult in Crohn's disease is in the epithelial layer of the intestine. We found small areas of epithelial necrosis, which we call patchy necrosis, in regions of the bowel that did not show acute inflammation and sometimes showed no inflammation at all.

Fig. 7 is a sample of intestine, of ileum from a

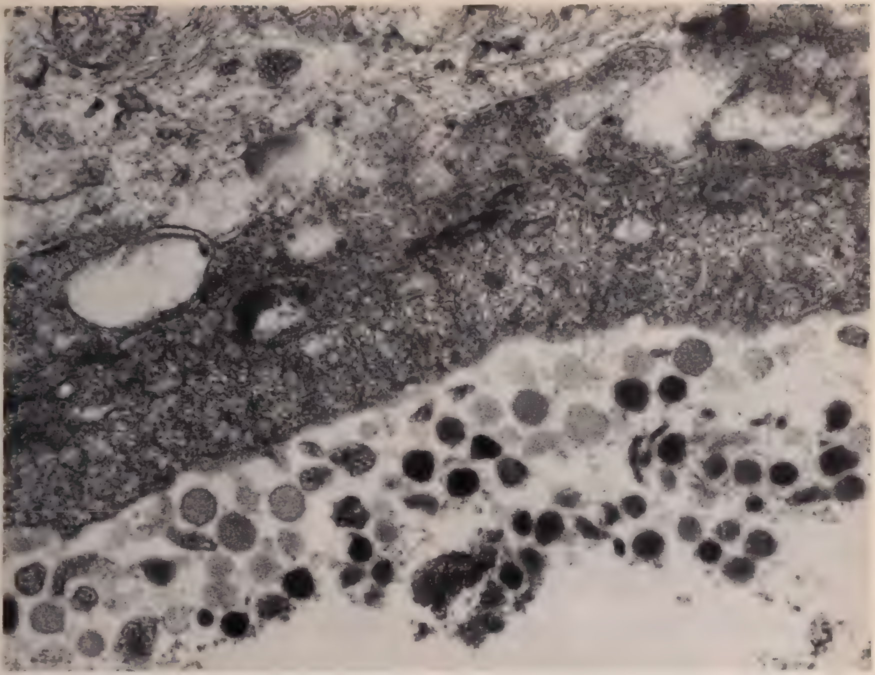

FIG. 4. Electron micrograph of a section of surgically removed ileum grossly unaffected by inflammation, from a patient with Crohn's disease. Visualized here is the lumenal aspect of the intestinal mucosa, which would normally be lined with microvilli. In their place are membrane-coated particles that have dense centers, and bud free from the epithelium. Magnification, 38,780×.

surgical specimen, near the resection margin which was grossly, microscopically uninvolved. We see a cell which is undergoing necrosis with abnormal microvilli and another fairly normal cell. Fig. 8, from biopsy from the rectum of a patient with Crohn's disease, shows necrosis of the epithelium and an area right next to normal-looking epithelium, which we call patchy necrosis. We are engaged in studying this finding at greater depth here at Mount Sinai. If it is fully confirmed it will have important implications for microbial etiology in Crohn's disease. We have already demonstrated that rotavirus multiplies in the epithelial layer of the human gut, and it would simplify matters to point to the epithelial layer as the origin of the disease in Crohn's disease.

I have mentioned our efforts at isolation of viruses using intestinal organ culture and direct examination of Crohn's disease tissues by electron microscopy. Another approach is to look for microorganisms, a method that has been very fruitful in the study of diarrheal viruses. In order to avoid the large intestine's massive growth of bacteria, we have chosen to examine the effluent from the ileostomies of patients with Crohn's disease using a refined method of differential and density gradient centrifugation to purify particles of the appropriate density and size. In just two cases of about twenty examined, we found particles that had an approximate density of 1.30, varied in size from 100 to 200 nanometers, and had a membrane and a dense core.

A section of a pellet from such a purified preparation of ileostomy fluid is shown in Fig. 9. The particles have a dense core and have a membrane surrounding them. However, they vary in size and would appear to fit a classification of either *Mycoplasma* or an L-form bet-

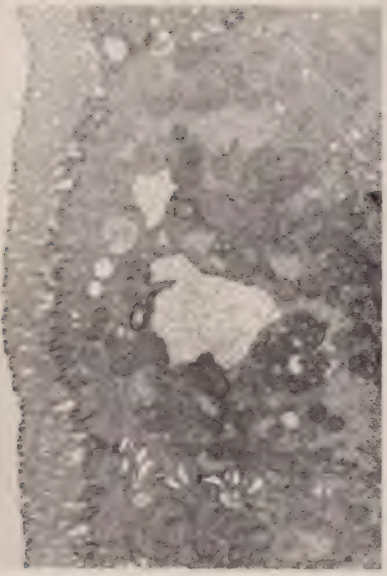

FIG. 5. Electron micrograph of a section of an organ culture of human fetal intestine, maintained in vitro for 30 days. The brush border consists of regularly arranged microvilli, and in the cytoplasm are seen many mitochondria and glycogen particles. Magnification, 8,300×.

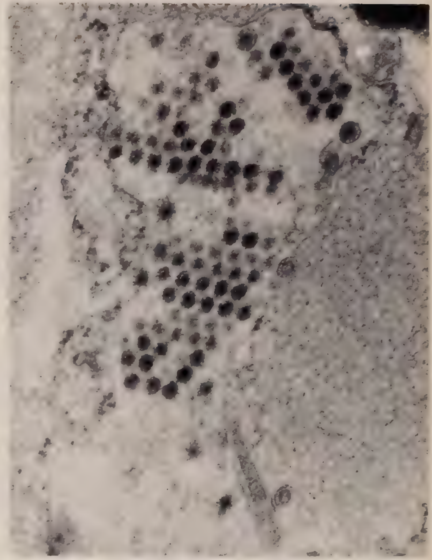

FIG. 6. Electron micrograph of a section of human fetal organ culture, infected with rotavirus for 3 days. There are symmetrical arrays of virus particles in the process of being assembled. Magnification, 51,600×.

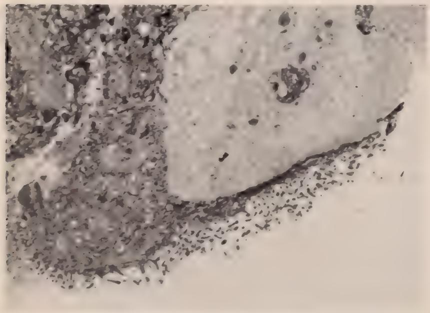

FIG. 7. Electron micrograph of a section of surgically removed ileum that was grossly unaffected by inflammation, from a patient with Crohn's disease. Individual damaged cells are seen adjacent to normal cells, with normal microvilli. Magnification, 4,675×.

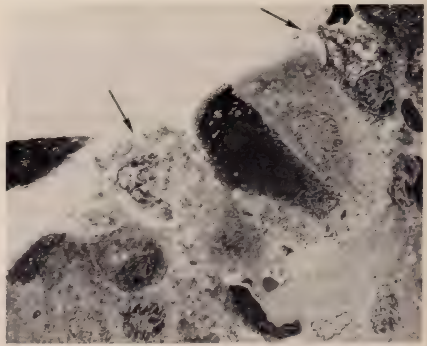

FIG. 8. Electron micrograph of a rectal biopsy from a patient with active rectal Crohn's disease. Arrows point to damaged cells near fairly normal-appearing epithelial cells. Magnification, 2,000×.

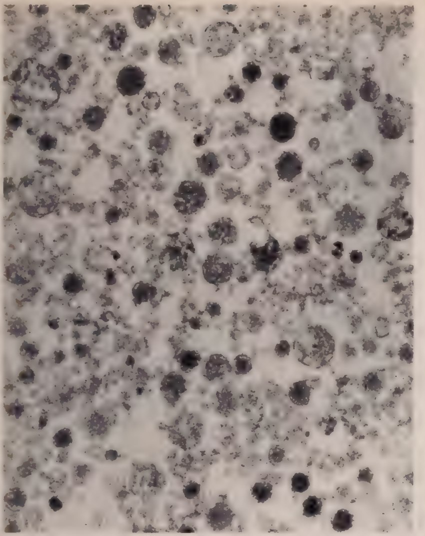

FIG. 9. Electron micrograph of a section of a preparation of density gradient purified particles from the ileostomy effluent of a patient with active Crohn's disease. Magnification, 20,500×.

ter than a virus. I have no data on the association of these particles with Crohn's disease, or their biological character, other than that they were from patients with active recurrent disease. I would guess that if these are microorganisms, they would, as I said before, belong to either *Mycoplasma* or L-forms. We are at a crossroads in the study of microbial agents in Crohn's disease. Our old concepts of just a year or so ago have to be discarded and we are trying new methods and new ideas in what is needed—patient, serious research.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Immunologic Approaches: Prediction of Early Recurrence in Crohn's Disease

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The surgical treatment of Crohn's disease is impaired by the significant number of recurrences that develop even after removal of all visibly diseased bowel. Although the overall recurrence rate is proportional to the amount of time elapsed, 30% to 40% of patients have recurrent disease within three years of surgery (1). At the present time, clinical and histologic criteria are not available to determine which patients have this aggressive form of the disease and are therefore likely to develop earlier recurrences (2).

Direct measurement and immunofluorescent studies (3, 4) have shown that there is a marked increase in the amount of immunoglobulins present in bowel affected with Crohn's disease. This is produced by large numbers of lymphocytes which are present throughout all layers of the bowel wall. Cells producing immunoglobulin G are predominant and can be increased over sixtyfold in severely inflamed areas (5). Since recurrences usually occur at the site of previous anastomosis, measurement of immunoglobulin concentrations at the resection margins and diseased tissues may provide an indication of disease activity and early recurrence potential.

Materials and Methods

Fifty-one patients with Crohn's disease operated on at The Mount Sinai Hospital between October 1978 and December 1981 were included in this study. Full thickness tissue specimens were obtained from the diseased portion and from the proximal resection margin. Normal samples from 20 patients with colon cancer and benign noninflammatory diseases served as controls. Histologic examination confirmed the diagnosis of Crohn's disease and found the resection margins and control tissue to be free of disease.

Extraction of immunoglobulin G was performed by tissue homogenization, followed by centrifugation at 250 times gravity for five minutes, then 100,000 times gravity for one hour. The supernatant was then dialysed against tris-HCl buffer (pH 7.5) for 12 hours and lyophilized for 48 hours. This produced a dry powder which was accurately weighed. After redissolving in one milliliter of normal saline, the immunoglobulin G concentration was determined by the radial immunodiffusion method. Low concentration agar gel plates were used and incubated for 48 hours at 37°C. Results were calculated in milligrams of immunoglobulin per gram of tissue dry weight. All patients were followed by their private physicians who were unaware of the tissue immunoglobulin G concentrations. Recurrences were diagnosed in symptomatic patients by barium studies, endoscopy, or reoperation.

Results

The mean immunoglobulin G concentration of the control tissues was 12.1 ± 4.2 mg/gm dry weight, with a range from 5 to 18. The proximal resection margin values of the Crohn's disease patients had a mean of 18.5 ± 8.7 and ranged from 5 to 42. Twenty of these samples (41%) had immunoglobulin G concentrations above the upper limit of the controls (see Figure 1). The mean diseased tissue immunoglobulin G value was 30.8 ± 10.7 and although these results were usually higher than the margin values, there was considerable overlap. There was no significant difference in the immunoglobulin G values for those patients receiving steroids, those having secondary surgery, and those found to have granulomata in the resected tissue (see

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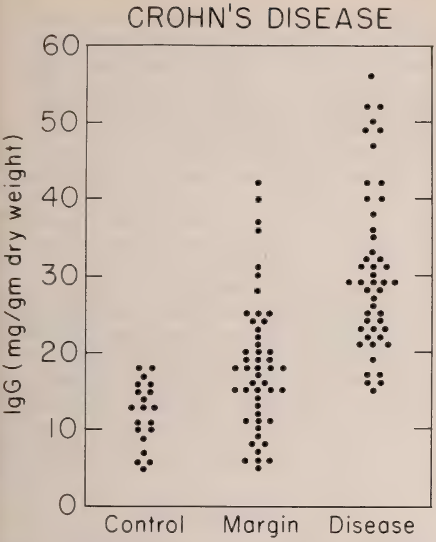

FIG. 1. Immunoglobulin G concentration in the control tissues, normal-appearing margins and diseased tissue samples of patients with Crohn's disease.

Table I). There was no correlation between margin or diseased tissue immunoglobulin G and age, duration of disease, or number of previous operations.

Thirty-eight patients have been followed from one to three years. Eleven (29%) developed recurrent disease (see Table II). The mean immunoglobulin G concentration of the patients with recurrence was significantly higher in both the margin and the diseased tissues (See Table III). Nine patients with recurrence had immunoglobulin G values of 18 mg/gm dry weight or higher. This corresponds to the upper limit of the control tissue values. Forty-seven percent of patients with margin immunoglobulin G concentrations above this level have developed recurrent disease within one to three years, as opposed to only 10% of those with values under 18 ($\chi^2 = 6.27$, $p < 0.05$). Fifty-three percent of patients with diseased tissue values over 30 have also developed recurrences, in contrast to 5% of those with lower concentrations ($\chi^2 = 10.17$, $p < 0.01$); see Figure 2.

TABLE I

Tissue Immunoglobulin G Values
51 Patients with Crohn's Disease

	Preoperative Steroids *Margin/Disease*	Previous Recurrence *Margin/Disease*	Presence of Granulomata *Margin/Disease*
Yes	17/32	19/30	20/30
N (%)	*28 (55)*	*21 (41)*	*20 (40)*
No	20/30	18/31	17/30
N (%)	*23 (45)*	*30 (59)*	*31 (60)*

TABLE III

*Immunoglobulin G Values, Patients with Recurrence**

	Yes	No	
Margin	24 ± 8	16 ± 8	$p < 0.05$
Disease	42 ± 9	29 ± 9	$p < 0.001$
N (%)	11 (*29*)	27 (*71*)	

* Patients followed for one year or more.

Discussion

Immunoglobulin G constitutes 70% of the immunoglobulins present in intestinal extracts of patients with Crohn's disease. It is markedly elevated in the diseased bowel and in many normal-appearing resection margins. There is a direct correlation between the immunoglobulin G concentrations in the margins and the

TABLE II

Data on Recurrence in 11 Patients

Patient No.	Date of Surgery	Site of Recurrence	Diagnostic Test	IgG Margin	IgG Disease
1	10/78	Anastomosis	Barium study	24	52
2	12/78	Anastomosis	Endoscopy	23	52
3	12/78	Anastomosis	Barium study	25	33
4	1/79	Ileostomy	Surgery	16	47
5	3/79	Anastomosis	Barium study	25	—
6	2/79	Anastomosis	Barium study	19	40
7	2/79	Anastomosis	Barium study	18	36
8	4/79	Anastomosis	Barium study	15	40
9	6/79	Anastomosis	Barium study	18	25
10	11/79	Anastomosis	Barium study	36	56
11	11/79	Anastomosis	Barium study	25	42

diseased tissues. Patients with higher values appear to have a more aggressive form of the disease and are prone to develop early recurrences. Immunoglobulin G concentrations of 18 mg/gm dry weight or higher at the margins, or above 30 in the diseased tissue, carry a high risk of early recurrence.

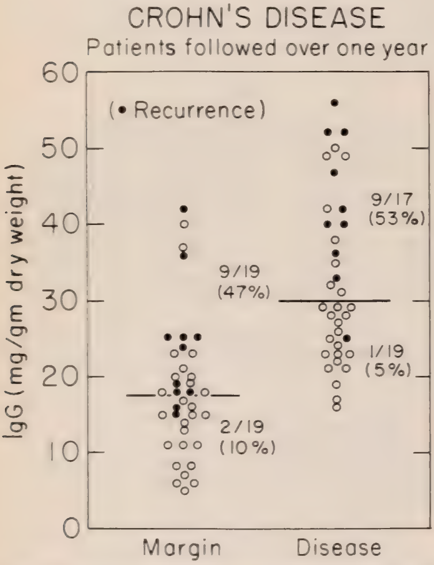

FIG. 2. Recurrence rates for patients followed from one to three years. Forty-seven percent of those with margin values of 18 or higher, and 53% of those with diseased tissue values above 30, have developed recurrent disease.

The fact that 41% of normal-appearing resection margins have elevated immunoglobulin G content is further evidence that gross inspection and histologic examination are not sufficient to detect disease activity. Furthermore, since recurrences usually occur at the anastomosis, it seems that the disease was present in latent form at the time of resection and that the surgical procedure stimulates it to become clinically apparent. At the present time, medical treatment of Crohn's disease consists of immunosuppressive medication. It is interesting to note, however, that there was no decrease in tissue immunoglobulin G concentration in patients receiving steroids preoperatively. Whether prophylactic treatment following surgical resection would be useful to diminish recurrence rates in this high-risk population remains to be seen.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

IBD in Families, Pregnancy, and Childhood

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In the fifty years since the description of regional ileitis was presented by Dr. Crohn to the annual meeting of the American Medical Association in New Orleans (1) the concept of granulomatous inflammation involving all segments of the alimentary canal has gradually become recognized and the terminology Crohn's disease has been accepted to describe the disease wherever it is.

Epidemiology

In 1932 it would seem that Crohn's disease was uncommon in comparison to ulcerative colitis. In fact over the last five decades the ratio of ulcerative colitis to Crohn's disease has changed from 4:1 to 3:1 to 2:1. Based on my own study of Crohn's disease as seen in private practice in New York City (2), the incidence has increased similar to that experienced in Scotland, England, Sweden, Norway, and Holland. Currently Crohn's disease is more common in New York than ulcerative colitis (when ulcerative proctitis is excluded) (Table I). This study also lends support to earlier studies showing that Crohn's disease is more common in females than males. In ulcerative colitis the sex ratio is approximately equal, except in proctitis, in which the incidence in females is higher. As suspected from previous reports of ethnic distribution, all forms of inflammatory bowel disease are more common in Jews than in other ethnic groups (Table II). It was often suspected that this was best explained by the fact that the early studies of IBD were reported from Jewish hospitals and other large institutions in eastern seaboard cities and in Chicago, where the percentage of Jews in the population is high. In New York, however, the incidence of Crohn's disease among non-Jews has increased parallel to the increase among Jews. An interesting observation has been that the increase among non-Jews has clearly supported the female preponderance, females accounting for 65 percent of the Crohn's disease cases among non-Jews. In contrast, ulcerative proctitis is four times as common among Jewish females as among non-Jewish females. Otherwise the increased incidence of Crohn's disease seems to parallel the ethnic population of the region, as shown by the low incidence among Jews who live in Houston, where the population of Jews is also low (Table III).

Children and IBD

Clinical observation substantiated by some objective data suggests that Crohn's disease is more virulent in children than in adults (3). Children require surgical resection more often and once surgery has been performed the proximal extension and the need for further surgery soon follows. Furthermore, pediatricians and other managing physicians are particularly fearful of using immunosuppressive drugs to treat children, despite the likelihood that it is these youngest patients who will do the best. In the New York study, children aged 15 and under account for 27% of patients with Crohn's disease (Table IV); the increase in incidence of Crohn's disease is accounted for by the age group 16–21 (Table V). Though the incidence in very young children has not increased, earlier diagnosis may yet reveal a still younger age of onset.

Ulcerative colitis too is more virulent in children than in adults. Children are subject to greater need for surgical intervention and a higher mortality rate than adults (4). In this disease the most severe symptoms occur in the early years. If these symptoms are tolerated, the patient is likely to do better in his or her twenties and thirties; unfortunately, the risk of

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TABLE I
Diagnostic Distribution of IBD New York City (1960–1978)

	Total	Male	Female
Ulcerative colitis	302	155	147
Ulcerative proctitis	94	41	53
Crohn's disease	321	147	174*
Indeterminate	32	13	19

* 57% were female.

TABLE III
Religious Background and Race: 261 Patients with IBD at Kelsey Seybold Clinic, Houston, Texas

Religion	%	Race	%
Protestant	64	White	94
Catholic	25	Hispanic	4
Jewish	8	Black	2
Other	3		

carcinoma of the colon rises while the symptoms fall. In contrast, there is no cooling-off period for Crohn's disease, which produces renewed virulent activity throughout a lifetime.

Children with IBD, both Crohn's disease and ulcerative colitis, are subject to one complication not seen with onset as an adult: retarded growth and development (5, 6). This often precedes the onset of the primary bowel symptoms (6). Growth failure often responds to effective medical management, just as do other manifestations of the disease. If not, surgical resection of the disease is usually followed by a growth spurt if resection is not delayed too long beyond puberty. The specific mechanisms of growth failure have been studied in recent years; whereas primary endocrine abnormalities have no role, inadequate intake due to symptoms, defects in absorption, and excessive losses in the stool all seem to contribute. When drug therapy alone is not satisfactory to reverse a trend of retarded growth and development, total parenteral nutrition may serve to accomplish this goal (7). In less severe cases even oral nutritional supplements in the form of elemental diets have a role (8).

Young children with inflammatory bowel disease are subject to emotional trauma which causes even greater complications than in adults. During the years of body and personality development, in which problems can arise under the best of circumstances, children are also subject to the symptoms of the disease, the side effects of drugs—including deformities of appearance accompanying corticosteroids—and frequent invasive diagnostic procedures, as well as the possible retardation of development. All of these considerations must be handled with great sensitivity on the part of parents, teachers, and managing physicians. In this regard the National Foundation for Ileitis and Colitis has been extremely helpful, with its self-help groups, educational sessions, and informative brochures.

Perhaps the most vexing problem regarding onset of Crohn's disease in childhood is late diagnosis. Pediatricians inundated with complaints of cramps and diarrhea will often postpone diagnostic evaluation when symptoms are modified by nonspecific agents. In ulcerative colitis when sigmoidoscopy is performed, the diagnosis is likely to be made. In Crohn's disease, however, where the rectal mucosa will probably appear normal, the diagnosis may be postponed for years. In the case of ileitis the small-bowel lumen may be narrowed close to obstruction before diagnosis.

Families and IBD

In the study of Crohn's disease in New York City (2), 20% of the patients had one or more blood relatives who suffered from IBD, usually Crohn's disease but sometimes ulcerative colitis (Table VI). Table VII shows the number of family relationships in the Crohn's disease pa-

TABLE II
Ethnic Distribution of IBD New York City (1960–1978)

	Jewish	Non-Jewish	Italian	Irish	Black
Ulcerative colitis	224 (74%)	78	25	10	2
Ulcerative proctitis	73 (74%)	25	8	3	2
Crohn's disease	230 (71%)	91	23	10	4
Indeterminate	17	13	3	2	0
	544	207			

TABLE IV
Age at Onset, Crohn's Disease
Private Practice, New York City (1924-1979)

Age Range	No. of Patients	
4-10	24 (7%)	56%
11-15	68 (20%)	
16-21	101 (29%)	
22-30	89 (26%)	
31-49	42 (12%)	
50-65	19 (6%)	
	343	

TABLE V
Changes in Age at Onset, Crohn's Disease
Private Practice, New York City

Age Range	1949-1964	1972-1978
4-10	8 (6.6%)	6 (6.2%)
11-15	23 (19.1%)	19 (19.6%)
16-21	32 (26.6%)	31 (32.0%)
22-30	32 (26.6%)	27 (27.8%)
31-49	14 (11.6%)	10 (10.3%)
50-65	11 (9.1%)	4 (4.1%)
	120	97

tients. The most common suggest a polygenic type of inheritance, those at greatest risk being those who share the most genes with the patient (9). Patients with Crohn's disease have many relatives with ulcerative colitis as well as Crohn's disease, whereas patients with ulcerative colitis have many relatives with ulcerative colitis but few with Crohn's disease. It may be postulated that Crohn's disease results from a larger concentration or summation of genes, and ulcerative colitis from a lesser (10).

Familial Crohn's disease and ulcerative colitis occur most commonly among Jews (80% of the families) (2). Two families with three generations of Crohn's disease were Jewish. One family with eight members suffering with Crohn's disease was Jewish.

Only four instances have been reported of Crohn's disease in husband and wife (2, 11-13). In one instance, one of two children has also developed Crohn's disease (2).

Families with members who have IBD are often emotionally disrupted and even devastated. This is particularly true when the patient is a child. This situation is probably true with any chronic disease and often the patient who suffers with the IBD is emotionally the most healthy member of the family. In this regard a skilled psychotherapist is often helpful. The situation often favors the choice of a family therapist who treats all members of the family together.

TABLE VI
Family Relationships in 72 Patients
with Crohn's Disease

	Crohn's	Crohn's vs Ulcerative Colitis	Possible Crohn's
Father—Daughter	13	3	1
Father—Son*	8	3	1
Mother—Daughter	5	2	2
Mother—Son*	3	3	
Brother—Sister	14	1	
Brother—Brother	6	2	
Sister—Sister	4	2	
Grandparents—Grandchild*	3	1	1

*Three generations of Crohn's disease in 2 families.

Pregnancy and IBD

Both Crohn's disease and ulcerative colitis are primarily diseases of young people. Since the prevalence of these diseases in the United States is probably greater than 1 million people, half of whom are female, the occurrence of pregnancy in women with these diseases should be expected with some frequency. Approximately 25,000 women will have a pregnancy after the ulcerative colitis or Crohn's disease has become established. Many issues arise in regard to management and prognosis of ulcerative colitis and Crohn's disease and pregnancy. The following are those most commonly raised by the patient, the family, or the managing physician.

Fertility. Statistically, there is no suggestion that women who have either Crohn's dis-

TABLE VII
Number of Family Relationships
353 Patients with Crohn's Disease

No. Relatives	No. Families
0	281
2	36
3	15
4	3
8	1

ease or ulcerative colitis are infertile or subfertile, since the rate of conception is within the range of the average population. Based on clinical observations, however, those with Crohn's disease may have some difficulty conceiving. This is rarely due to blockage of the fallopian tubes by adhesions, as suggested in the older literature, but more likely is associated with overt Crohn's disease activity. There is some evidence that a problem in conception is more likely to arise in patients with colonic involvement (Crohn's colitis and ileocolitis) rather than ileitis.

Risk of Inheriting the Disease. In anticipation of pregnancy, most women with IBD will ask questions about this. What is known has been summarized in the section on Families.

Influence of IBD on Pregnancy. The evidence from studies reported over the last 25 years has been consistent in concluding that neither disease has an unfavorable effect on the outcome of pregnancy. The figures for incidence of premature births, spontaneous abortions, stillbirths, and congenital anomalies have been much less than those reported in general populations. Nevertheless, based on a recent national survey (14), the rate of spontaneous abortion is much higher in active Crohn's disease than in the overall Crohn's disease population. This is further emphasized by an ongoing study at Lenox Hill Hospital. In specific patients who develop severe complications, such as intraabdominal abscess or obstruction requiring operative intervention, the risk to the fetus climbs precipitously.

Although there is less evidence of risk to the outcome of pregnancy in ulcerative colitis, congenital anomalies have been observed. Furthermore, there is an increased risk of prematurity and spontaneous abortion (not as high as in Crohn's disease) in the presence of active disease as opposed to inactive disease. Similar to the situation in Crohn's disease, if the course of the disease is severe during the pregnancy, if a complication such as toxic megacolon develops, or if surgical intervention is required, the risk to survival of the fetus increases accordingly.

Influence of Drug Therapy on Pregnancy. The drugs most commonly used in the treatment of inflammatory bowel disease are sulfasalazine, ACTH or adrenal steroids, and the immunosuppressives (6-mercaptopurine or azathioprine). Sulfasalazine was previously thought to be responsible for an occasional case of kernicterus; this has not been supported by the present study. Sulfasalazine may interfere with folic acid absorption. Furthermore, it frequently has been responsible for side effects such as headache and nausea, although these usually subside after the patient has adjusted to the drug or the dose is reduced to a tolerable level. Because of these various considerations, the pregnant patient with inflammatory bowel disease often wishes to stop the sulfasalazine since she fears the fetus will be harmed. The obstetrician, as a generality, makes little effort to encourage continuation of the drug, despite its prophylactic value in preventing recurrence of the inflammatory bowel disease. Evidence drawn from the national survey, however, warrants a conclusion that the fetus is not in any way harmed by sulfasalazine, nor is the newborn harmed during nursing in the postpartum period (14).

The situation is similar with steroids. While there are theoretical risks to high-dose or maintenance steroids, there has been no evidence of damage to the fetus attributable to these drugs. As mentioned above, the danger of complications to the pregnancy parallels the severity of the disease and not the drugs used in its treatment.

With immunosuppressives there is a theoretical consideration of chromosomal damage and therefore of fetal deformity. Since experience with immunosuppressives and pregnancy remains limited, patients have been advised not to become pregnant while taking these drugs. Should a patient become pregnant while taking immunosuppressives, therapeutic abortion has been advised.

Influence of Pregnancy on IBD. Reports dating back 25 years, when patients with inflammatory bowel disease received either low-dose steroid therapy or no significant treatment at all, suggested that the influence of pregnancy on the course of the disease could usually be correlated with the activity of the disease at the time of conception. In ulcerative colitis, if the disease was quiescent at the onset of pregnancy, the odds favored it remaining so throughout (15, 16). If, on the other hand, the disease was active, it would likely continue to be active or even worsen during the pregnancy.

Current data support these earlier observations, with one important exception. Should the patient with active ulcerative colitis be brought into remission with drug therapy, the prognosis improves so that it is similar to that of the patient whose disease was quiescent at the onset of pregnancy (17). If there should be an exacerbation or worsening of the disease during pregnancy, it is most likely to occur during the first trimester.

Based on early reports, the situation of patients with Crohn's disease was different. If the disease was quiescent at the time of conception, it was likely to remain so throughout the pregnancy (18, 19). On the other hand, if it was active at conception, the odds favored improvement during the pregnancy. Evidence derived from more recent studies does not support these earlier findings but rather likens the course of Crohn's disease during pregnancy to ulcerative colitis (17). In other words, if the disease is active at the outset, it is likely to remain so, or to worsen. The difference in results between earlier and later studies has not as yet been explained but may be influenced by changing attitudes toward surgical resection and drug therapy during the course of Crohn's disease. Should there be an exacerbation or worsening of Crohn's disease, it is most likely to happen during the third trimester.

Influence of Postpartum Period on IBD. According to early reports, exacerbation of Crohn's disease occurred frequently in the postpartum period and often required high-dose steroid therapy (18, 19). This was not true for ulcerative colitis (15, 16). The results of recent studies differ by showing the status of both diseases is influenced by the state of disease during the last month of pregnancy (17, 20).

IBD with Onset During Pregnancy and Postpartum Period. Cases of inflammatory bowel disease having onset during pregnancy were previously described as fulminating and carried a poor prognosis, especially in ulcerative colitis (16), whereas a recent report concludes that ulcerative colitis starting during pregnancy is no worse than when onset is at any other time (20). Studies reported since 1950 have included so few patients with Crohn's disease having onset during pregnancy, or with either disease having onset in the immediate postpartum period, that no conclusions can be reached about these associations.

Previous Bowel Surgery and Pregnancy. There appears to be no unfavorable influence of previous bowel resection either for Crohn's disease or for ulcerative colitis on the course of pregnancy. Patients with ileostomies for ulcerative colitis (or sometimes for Crohn's disease) occasionally suffer ileostomy prolapse or obstruction during the pregnancy. It is best to postpone pregnancy for a year after the ileostomy is constructed (whether conventional or continent ileostomy), to allow for adaptation. In Crohn's disease complicated by perirectal abscesses or fistulae, an episiotomy sometimes has to be avoided, requiring that the delivery be by cesarian section.

Prognosis for Future Pregnancies. There is no evidence that the course of either ulcerative colitis or Crohn's disease during one pregnancy will be the same during subsequent pregnancies.

Therapeutic Abortion and IBD. In the past, a severe exacerbation of ulcerative colitis was occasionally treated by therapeutic abortion. The results were mixed, in that the disease improved in some but not all cases. Currently there is rarely an indication for therapeutic abortion.

Bowel Surgery During Pregnancy. Surgery should be postponed until after delivery if at all possible. If, however, the indications for surgical intervention are clear for either ulcerative colitis or Crohn's disease, surgery should be performed. Although the likelihood of survival of the fetus is reduced because of the surgery, the outcome would be even worse were surgery not performed for fulminating disease not responding to medical management.

Diagnostic Procedures During Pregnancy. There is no contraindication to sigmoidoscopy, rectal biopsy, or gastroscopy if indicated for proper management during the course of pregnancy. A limited flexible colonoscopy may be feasible if the clinical situation warrants it. Diagnostic x-rays should be avoided during the first trimester and preferably postponed until after the delivery.

Current Medical Management During Pregnancy. The medical management of inflammatory bowel disease should include the following:

1. If either disease is active at the time of conception, it should be treated vigorously with steroids to bring it into remission. The favorable outcome of the pregnancy and the later course of the disease depend on the resulting quiescence. Sulfasalazine may then be introduced if not previously established as part of the program.
2. If the disease is quiescent and the patient is receiving sulfasalazine, the sulfasalazine should be continued throughout the pregnancy and the postpartum period.
3. If either disease should exacerbate during the pregnancy, again it should be treated vigorously with steroids to accomplish a remission. Again, sulfasalazine may then be intro-

duced if not previously established as part of the program.

4. If the disease is active, it should be treated and brought into remission if at all possible prior to planning a pregnancy.

5. If a patient with ulcerative colitis or Crohn's disease cannot conceive and there is any indication of active disease, that patient should be treated more vigorously until the disease is clearly brought into remission.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

Sexual Dysfunction after Colectomy

JOEL J. BAUER, M.D.

An experience with a patient two years ago got me interested in studying the postoperative sexual function, or really the sexual dysfunction, of the patients in our practice. A young man in his 30s who had had ulcerative colitis with moderate activity for approximately ten years was sent by his gastroenterologist to a surgeon. The gastroenterologist advised colectomy. The surgeon told this young man that the chance of his becoming impotent after proctocolectomy was in the neighborhood of 25%. Because of this comment, the young man was not happy about undergoing surgery at the time. Two years later, he appeared in our office with carcinoma of the splenic flexure. He underwent surgery, and was fortunately not rendered impotent, but did have several mesenteric lymph nodes that contained metastatic adenocarcinoma. This situation got me very interested in the study of sexual dysfunction because it was my impression, at the time, that the incidence of impotence in the patients who had been operated on by myself and my associates was much, much lower than the 25% incidence sometimes quoted in the literature of the 1960s. Much of that literature was really based upon experience with abdominoperineal or rectal resection in carcinoma of the rectum. The operation for carcinoma is a totally different operation, requiring wide dissection of tissues, especially posterior, with almost certain pelvic nerve injury. In addition, carcinoma is a disease of much older people and many subsequent studies have shown that the rate of impotence, even in patients with ulcerative colitis, is definitely age-related. I think the problem which this unfortunate man encountered was that his gastroenterologist and his surgeon based their impressions on the older literature.

I discuss here the experience with approximately 300 patients in our practice who have undergone proctocolectomy for benign disease of the rectum and colon. We have made attempts in our procedure to avoid injury to the nerves, the parasympathetic and sympathetic nerves, which govern sexual function. Some of the patients included had familial polyposis. The vast majority had ulcerative colitis; a few had Crohn's disease.

Sexual dysfunction following proctocolectomy can be separated into dysfunction of organic and dysfunction of psychogenic origin. I confine the majority of my remarks here to the organic causes and only touch on some of the psychogenic or sociosexual causes. The organic causes—that is, the anatomic injuries which may occur during proctocolectomy, and the physiologic sequelae which follow—form the basis of this talk. For the best understanding of the problem, a brief review of the pertinent anatomy is in order.

Anatomic Structures and Operative Procedure

Sexual function in men, and in women also, is related to both the sympathetic and the parasympathetic nervous system. Most of my remarks concern impotence and retrograde ejaculation in men. I also touch on some sexual dysfunctions in women.

The sympathetic chain passes just anterior and lateral to the aorta and gives off fibers from the lower thoracic and upper lumbar branches, which then go down to an area just at the bifurcation of the aorta, which is relatively close to the sacral promontory. All the problems and injuries occur in the pelvis. This, then, gives off branches which form the hypogastric plexus, proceeding thence into the pelvic plexus, or what is called in the British literature the inferior hypogastric plexus. The nerves in this area run lateral and slightly posterior to the rectum; these give off branches to the bladder, to the seminal vesicles in men, to the vas deferens, and thence to the prostate and bulbo and corpora cavernosum. The nerves that we are most

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fearful of injuring, and take great effort not to injure, are the nervi erigentes, which come off the lumbosacral plexus. That is the main pelvic parasympathetic supply, and injury to these nerves in this region will cause impotence in men. Ejaculation is governed mostly by the sympathetic nerves, which are occasionally injured in the area near the bifurcation of the aorta. There is tremendous fusion of the nerve supply in this area. The true anatomic nervi erigentes are these nerves, exiting from the sacral foramen. However, most surgeons refer to this entire plexus of nerves as the nervi erigentes. The pudendal nerve is rarely injured during surgery, because it is covered by dense endopelvic fascia; this nerve channels sensory supply to the penis and labia and also stimulates contraction of the ischiocavernosus and bulbocavernosus muscle during ejaculation. I've never heard of this nerve being injured during proctocolectomy.

The main sites of injury are really a result of dissection which goes too far away from the colon wall. This kind of dissection is necessary in a so-called "cancer operation," but is totally unnecessary in any operation for benign disease of the rectum. Injury occurs largely in the area of the preaortic or hypogastric plexus, and injury here can actually cause pure sympathetic denervation. Patients with such an injury frequently suffer from retrograde ejaculation because of the failure of the bladder sphincter to contract during ejaculation. These men really ejaculate into their bladder. They are still able to have orgasm, but cannot ejaculate. The other areas of injury are shown in Fig. 1. We know that men frequently become impotent simply from interruption of these nerves, because in perineal biopsy of the prostate or perineal prostatectomy, impotence is a rather common complication.

Very little has been written about sexual dysfunction in women; certainly its anatomic or physiologic basis has been very little discussed. The erectile function of the clitoris is dependent, just as erectile function is in the male, on the nerve and the vascular supply. We have found that after removal of the rectum, some patients sustain retroflexion and retroversion of the uterus or impingement of the posterior vaginal wall against the bony sacrum. Scarring is frequent in this area after removal of the rectum, and sometimes this is a cause of dyspareunia in some of our patients.

In the last ten years we have attempted to stay as close as possible, in the dissection of the rectum, to the rectal wall, so as not to injure this nerve supply. We do this in the abdominal portion of the operation by staying virtually on top of, or immediately adjacent to, the wall of the sigmoid colon and upper rectum, making no attempt to take any mesentery. In the rectal excision portion of the operation, we actually do an intrasphincteric excision of the rectum, working between the external and internal sphincters and the rectal wall. We leave behind the internal and external sphincters and levator ani (one of the main sphincters of the rectum); we stay adjacent to the rectum. After the removal of the rectum, the surgical field shows complete or almost complete sparing of the sphincters; obviously the sphincters are totally unimportant, but we attempt to avoid any injury to some of the periprostatic plexus in this area in men. Most of our closures are drained by a sump tube.

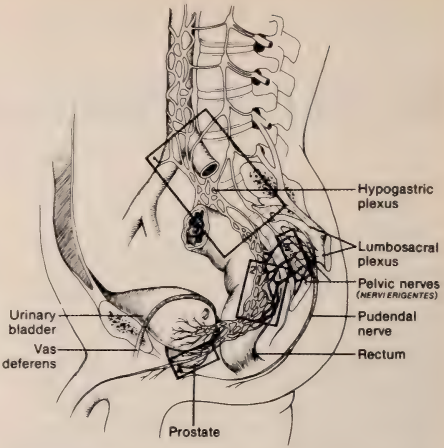

FIG. 1. Common sites of operative injury: 1 aortic and hypogastric plexus; 2 fusion of pelvic nerves and hypogastric plexus; 3 origin of pelvic nerves from lumbosacral plexus; 4 nervi erigentes in region of prostatic venous plexus.

Methods and Results

In the main, our study was prospective. We did do some retrospective analysis by sending out questionnaires to patients. Most of the questions addressed to the men were related to ability to have and sustain an erection, ability to ejaculate, and changes in sensation, however minor. The questions addressed to the women had to do basically with changes from the preoperative state, changes in sensation, especially dyspareunia.

Between 1973 and 1981, proctocolectomy was performed on 291 patients, our study series.

Of the 291, 135 were men. Five men were excluded because they did not have adequate sexual function preoperatively. These were men in their late 60s; one was in his 70s.

Approximately three quarters of all the patients in the study were actually interviewed personally by either myself or one of my associates in practice. In the men, we found permanent impotence in only two patients, an incidence of about 1.5%. The modern literature is now replete with studies which show a rate of impotence ranging anywhere from 4% to 15%—15% at the most. This is nowhere near the rate that was previously reported. Our incidence was 1.5%. In addition we found temporary impotence in one young man, who fully recovered four months postoperatively. In this series we could see no difference in the frequency of impotence relative to age. One of the permanently impotent men was 19 years old; the other was 44. Most of our patients were rather young, because most of them were operated on for ulcerative colitis. Two patients had retrograde ejaculation, also an incidence of 1.5%. These two were also relatively young.

The series of 291 included 156 women. Four of these women were sexually inactive preoperatively and during the followup period and they were excluded. Of the remaining 152 women, two suffered temporary dyspareunia. Both of these women sustained lacerations of the vagina during the removal of the rectum, which occurs occasionally during operation.

The one other finding has to do with the psychosexual or psychosocial implications of having a stoma. A large percentage of our patients had continent ileostomies. So, as Dr. Gelernt remarks, many of these patients did not have to wear an appliance, did not have the fear of an appliance dislodging during intercourse, did not suffer as much of the body-image problem that many of these patients have. In interviewing our patients, I began with a general question. I was impressed that the patients with the continent ileostomy suffered much less in the way of sexual dysfunction. Many of these patients, after all, had had an ileostomy for some time prior to conversion to a continent ileostomy, and most of them said that all of their relationships were much easier, now that they did not have to worry about appliances, stomas, and so on. But this is still an impression, and we have yet to really get our data together.

The Mount Sinai Journal of Medicine
Vol. 50. No. 2. March–April. 1983
Printed in U.S.A.

Assessing Quality of Life

Samuel Meyers, M.D.

Little attention has been paid to the assessment of the quality of life among patients with inflammatory bowel disease following either medical or surgical intervention. There are no rigorous studies concerning the psychosocial aspects of medical therapy. When considering surgical therapy we all know the life-saving role of emergency surgery for toxic megacolon, obstruction, perforation, or bleeding. Also well established is the curative role of proctocolectomy for ulcerative colitis, despite the obvious burden of the ileostomy. Many physicians, however, are reluctant to recommend elective surgery to their patients with Crohn's disease, chiefly because of concerns about postoperative recurrence. Despite recent advances in quantifying the risk of disease recurrence (1), there is little knowledge about the quality of life experienced by patients after surgery. Most studies have been retrospective chart reviews (2–11). Even when patients were evaluated by prospective interview, the criteria for the final assessment of their status was described in only general terms, or medical and surgical groups were not separated (9, 12–13). In spite of these limitations, most studies have agreed that long periods of good health appear to be achieved by 50%–87% of patients.

We were interested in answering the very important question of whether elective surgery for Crohn's disease provides satisfactory long-term palliation. We personally interviewed 51 patients five to ten years after their first elective operation for Crohn's disease (14). These patients had been seen on our private service at The Mount Sinai Hospital over a five-year period. Twenty-six patients had ileal disease and 25 had disease predominantly in the colon, 14 with some concomitant ileal involvement.

In our interviews, we evaluated overall patient satisfaction, specific symptoms, and five areas of psychosocial functioning: personal relations, school and job performance, recreation, sexual activity, and body image. Questionnaires were used consisting of 39 direct inquiries, each constructed with frequent and familiar words according to accepted sociological guidelines. Responses indicating dysfunction were classified as mild or severe. For each area, we tabulated the percentage of total responses indicating any degree of impairment. We inquired about function at three points in time: six months preoperatively, one year postoperatively, and at the time of interview, which was a mean of eight years after surgery, with a range of five to ten years.

One hundred percent of patients complained of some overall trouble preoperatively, severe in 77% of the ileitis and 88% of the colitis groups. In reports of postoperative functioning, these proportions progressively diminished for both frequency and severity, so that by the time of interview, dysfunction was reported by only 42% (14% severe) of the ileitis and 48% (12% severe) of the colitis group. These differences are significant at the $p < 0.001$ level. Forty-seven patients (92%) felt the operation had been helpful, and only four patients would not have agreed again to surgery: one because of difficulty with ileostomy, one on account of diarrhea, and two as a result of disease recurrence. Both the ileitis and the colitis group reported a progressive decrease in frequency and severity of dysfunction in each of the other specific areas assessed: physical symptoms, evaluated by 14 specific questions; personal relationships, assessed by the ability to visit and get along with friends and family; school and job performance, measured by questions about initiative, attendance, relationships, performance, and achievement; recreation, judged by participation in hobbies or sports, social functions, and civic work; sexual activity, measured by five specific questions concerning sexual interest, pleasure, and details of performance; and, finally, body image, derived from inquiries about 10 potential negative attitudes to self (Table I).

In general, then, our patients improved after

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TABLE I

*Percentage of Total "Dysfunction" Responses**

	Ileitis			(Ileo) Colitis		
Area of Dysfunction	Preoperative	1 Yr Postoperative	At Interview	Preoperative	1 Yr Postoperative	At Interview
Symptoms	48	24	18	55	21	17
Personal relations	62	27	19	84	30	24
School and employment	71	29	14	68	24	14
Recreation	69	33	29	89	48	20
Sexuality	52	26	6	61	22	6
Body image	37	20	10	40	30	24

* Adapted from Meyers et al (14).

TABLE II

*Percentage of Total "Dysfunction" Responses, (Ileo) Colitis Patients with and without Ileostomy**

	Ileostomy		No Ileostomy	
Area of Dysfunction	Preoperative	At Interview	Preoperative	At Interview
Overall	100	64	100	27†
Symptoms	63	19	45	18
Personal relations	86	29	82	18
School and work	86	15	53	11
Recreation	86	28	91	14
Sexuality	73	9	45	2
Body image	44	31	37	20†

* Adapted from Meyers et al (14).
† Difference from ileostomy group at interview: $p \leq 0.05$.

TABLE III

*Percentage of Total "Dysfunction," Patients with and without Disease Recurrence**

	Ileitis Group				(Ileo) Colitis Group			
	Recurrence		No Recurrence		Recurrence		No Recurrence	
Area of Dysfunction	Preop	Interview	Preop	Interview	Preop	Interview	Preop	Interview†
Overall	100	58	100	7†	100	67	100	20
Symptoms	52	35	45	4†	58	21	51	11
Personal relations	79	21	46	18	80	37	90	5
School and work	68	20	74	10	75	20	51	6
Recreation	100	37	50	23	88	38	90	0
Sexuality	63	7	42	5	55	8	61	6
Body image	41	12	34	9	47	33	30	10

* Adapted from Meyers et al (14).
† Difference from recurrence group at interview: $p < 0.05$.

surgery. But were these results influenced by the presence of an ileostomy? There were 14 patients with ileostomies, all derived from the colitis group. Although the results among these 14 patients were not quite as good as for patients without ileostomy, the group did report significant improvement. The data are shown in Table II. Among the 14 patients with ileostomies, at the time of interview dysfunction was significantly reduced compared to preoperative status in all seven areas assessed.

If the presence of an ileostomy did not prevent postoperative improvement, how about the influence of disease recurrence? There were 27 patients who suffered disease recurrence, 20 of whom had required one or more subsequent operations by the time of interview. Like the patients with ileostomy, the patients with recurrent disease had less postoperative improvement than those without recurrence. Yet, as we see in Table III, these 27 patients with recurrent disease reported significantly less dysfunction at the time of interview than preoperatively in all seven areas of assessment.

In summary, then, we found a sustained and progressive reduction in the frequency and severity of illness-related symptoms and psychosocial dysfunction among 51 patients who had had elective surgery for Crohn's disease. Ninety-two percent of the patients were satisfied that surgery met their expectations and would choose it again. Ileostomy and disease recurrence did have an unfavorable influence on functioning but still did not prevent improvement. Elective surgery in this selected group of 51 patients clearly improved their quality of life and thus proved to be justified as an alternative to continued medical therapy, from the patient's point of view.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 2, March–April, 1983
Printed in U.S.A.

The Next Fifty Years: Panel Discussion

MODERATOR: FRED KERN, JR., M.D. DISCUSSANTS: MR. JOHN ALEXANDER-WILLIAMS, ARTHUR H. AUFSES, JR., M.D., HENRY D. JANOWITZ, M.D., AND JOHN E. LENNARD-JONES, M.D., FRCP

Dr. Kern: I think we should move on to the final event on the program. I am sure we all want to know what's going to happen during the next fifty years. While the panel is assembling I would like to comment on my impression of the last day and a half. We really have learned a lot about inflammatory bowel diseases in the last fifty years. Despite the absence of an understanding of the causes of these diseases and our inability to cure them, we have acquired a great deal of information. Once again, I'd like to express my admiration for the group at Mount Sinai who have contributed so much to this body of knowledge.

I have asked each member of the panel to take about two or three minutes to speculate in broad, general terms about what they think will be the most important development during the next fifty years. I should caution them that people who live by the crystal ball often die of ground-glass poisoning. We'll go from left to right and start with Dr. Lennard-Jones.

The Shape of Things to Come

Dr. Lennard-Jones: I think that during the next fifty years we will discover that ulcerative colitis and Crohn's disease are different. I think that in ulcerative colitis, we'll take a particular interest in the bacterial flora of the gut and its relationship with the genetic immunological status of the host. I suspect that we'll find that it is changes in the bacterial flora of the gut that, in fact, decide remission and relapse, and probably the severity of the relapses. I think that in ulcerative colitis we'll understand a lot more about the pathogenetic mechanisms. That's not to say the cause of the disease, rather it is why it behaves as it does when the exciting trigger has been pulled. We'll learn a lot about prostaglandins, I think. We'll learn a lot about chemical transmitters in the gut wall.

As we look at treatment, medical treatment in particular, I think we'll find out how the treatments affect these pathogenetic mechanisms. There is a lot of interest at the moment in the way that sulfasalazine is affecting these pathogenetic mechanisms. I think we are going to find, perhaps, how steroids affect them also. I suspect that our medical treatment is going to improve because we are going to be able to design the treatment to affect those pathogenetic mechanisms which I've referred to. In particular, I think that we are going to perhaps use steroids rather more; these are just in their infancy at the moment. I think we are going to find, perhaps, why sulfasalazine protects patients against getting a relapse, and we can design better drugs than sulfasalazine for doing that.

Having said all this, I also think our surgical colleagues are going to develop more acceptable operations. I do accept entirely what's been said, that the reason the patients don't want surgery is that they don't want an ileostomy. I hope our surgical colleagues can make ileostomy more acceptable. But I don't think that continent ileostomy is the full answer. I think that the full answer is going to leave anatomy much more as it is, that is to say with the use of the anus. Then I think surgery will be more acceptable and I think we as physicians will be recommending it more frequently and our patients will be accepting it more readily.

With Crohn's disease, I think we're going to find that it has an infective basis. I think we'll also find that there is an environmental factor which accounts for differences in epidemiological incidence in various countries, and I think this epidemiology is going to be very important. One of the interesting things is going to be to see if it spreads much more worldwide than it is at the moment, and if the worldwide spread correlates with various environmental changes; perhaps, for example, in diet. I would be very interested in those studies which have shown that patients with Crohn's disease eat more sugar and more refined carbohydrates than other people. This is one of the constant features in epidemiological surveys. I think there are now six surveys which show this fact. I suspect that we are going to look at the genetic component in Crohn's disease and we are going to find an interaction, perhaps, between the particular immunological function of patients and whatever the environmental agent is.

As regards treatment in Crohn's disease, I do hope that we are going to see control data on whether bowel rest affects the inflammatory disease. I don't think we know this yet. I think we are going to have a lot more interest in antibacterial drugs, and we are going to want to know whether this is primary treatment or treatment of secondary infection. I'll leave it to others to comment on the surgical treatment of Crohn's disease.

Mr. Alexander-Williams: As a short answer to that, I'm going to tell you later what we're doing in Birmingham now. What surgeons have to learn is that Crohn's disease is panenteric. It's potentially a disease of the whole of the alimentary tract, and therefore you cannot possibly remove all the disease.

What will happen in the next fifty years is that surgical mortality will disappear. I think it will disappear probably in the next two or three years. When I started in this game in 1940 we had about 10% surgical mortality. In 1955 we had 5% surgical mortality in our Birmingham series. Ten years ago we had 2% mortality. In the last ten years we have had 400 major resections with 4 deaths. Analyzing these deaths in retrospect, they were all avoidable. I think that probably there will be no surgical mortality at all by 1985. I think that the other important thing we are going to learn is that we sacrifice as little tissue as possible. It has upset me to hear physicians talk at this meeting about taking out more and more and more gut, and rendering cripples. What we will learn is that you do not need to take out Crohn's disease to cure the surgical indications of stenosis and fibrosis. Look at what the Indians were telling us with tuberculosis some few years ago. They said, Now, we've controlled tuberculosis, all we have are the fibrous sequelae in the gut, and we just do strictureplasties on those. Could we not possibly apply that to Crohn's disease in the next fifty years? We do not really need to take out an area like that, which is producing very severe symptoms. (Slide) This is a patient with a recurrence after hemicolectomy for ileocecal Crohn's disease and there are two tight strictures in not very active disease. Now, what can you do for this patient? You take the stenosis, and make a longitudinal incision through it. Then you suture it transversely, suturing Crohn's disease in the form of a strictureplasty. This is very much like the Heinecke-Mikulicz pyloroplasty that you do for duodenal stenosis. (Slide) Here's a patient with multiple strictures. These multiple strictures actually had enteroliths between them. I took the enteroliths out and I passed a 25-mm sizing head from the EEA stapling machine, and ran it along the gut until I identified the site of the next stricture—you perform a strictureplasty on this. You can do this with skip lesions. This particular patient had nine strictures and between most of them there were large enteroliths. I performed nine strictureplasties on this patient. The gut is sewn transversely. I sew it up with one layer of continuous Vicryl. There is no need to turn it in. The tissue holds sutures beautifully. It's fibrous tissue and it is extremely easy to suture Crohn's disease to Crohn's disease.

If there is a much longer length of gut, 20 to 30 cm in length, as I've now had in three patients, and I was very anxious not to sacrifice gut, the procedure can still be done. You can bend it up sideways like a Finney pyloroplasty and I have done this on three occasions. (Slide) There is a Finney pyloroplasty at the site of a stenosis in a patient who was very short of gut and had a 30-cm stenosis proximal to the ileotransverse anastomosis.

Now the question is, if you do this, will it fistulate? Will it leak? Will the gut heal? So far, I've now done 30 short strictures and three long strictures and I can tell you that the sutures do hold. The suture line doesn't leak. We have had no leaks, we have had no fistulas, and we have no abscesses. I've operated on one patient a year later because there were other strictures that I wish I had done at the same time. I went back, and the first strictureplasty was still wide, it was absolutely supple and there was no indication of any active Crohn's disease at the site. So, that's all pretty encouraging. I think that this will be used increasingly in the coming years, I think particularly for very short strictures like those I've shown you, for multiple strictures, and certainly for skip lesions proximal to some major disease. I think it will be useful. It will be very useful for shortage of gut. On Tuesday of this week I operated on a girl who, if I had taken out her Crohn's disease, would have had only 80 cm left from her duodenojejunal flexure. She had three strictures throughout her gut and I performed a strictureplasty on each of them.

I think the great danger in the next fifty years is that physicians will get to hear of this, and they'll pass long dilating machines down the gut. Surgery will probably be superseded completely by physicians who are gently dilating strictures, which is, after all, the only indication for operations in Crohn's disease. If I look ahead and think what will I be doing in another fifty years, I think I shall still be doing the same thing. I shall still be operating. I shall still be being assisted in almost every move. But I hope that I shall still be as vigorous as Dr. Crohn is. I just want to say that in these next fifty years I think we are going to see wonderful examples of continued collaboration between physicians and surgeons and epidemiologists. I think, also, these inflammatory diseases are going to foster great international collaboration. I think bringing John Lennard-Jones and me here was a marvelous idea. We really appreciate it—and Crohn's disease certainly fosters international good will. Thank you.

Dr. Kern: Well, I'm sure we all agree that bringing John Lennard-Jones and John Alexander-Williams here was a great idea. And now, Dr. Janowitz.

Dr. Janowitz: Futurology is a very hazardous job. I think advances in our understanding are going to be along two lines. One is the kind of futurology we can talk about—that which is really the extension of the current line of investigation. The future is not identical with the past, but it certainly tends to resemble it. We are going to continue to have more studies on the natural history of the disease, including all the epidemiological and environmental factors that Dr. Lennard-Jones has talked about. We are going to have recognition of an increasing variety of infectious agents, so that the reservoir of nonspecific disease will shrink. I think it will be greater in Crohn's disease than it will be in ulcerative colitis. I think that we will discard from the Crohn's list those aphthous ulcers that are the results of other infections. I think that one of the important things we are going to learn, and will focus on, is the nature of acute self-limited colitis, about which we haven't talked very much in this meeting. Dameshek said that infectious mononucleosis was an aborted attack of acute leukemia. What we have to find out is whether some of these acute, active self-limited colitides are really abortive attacks of acute ulcerative colitis.

When I said we will learn more about the natural history of the disease, I want to point out that there are some aspects of the future that you can't predict. Patients are being observed not only by doctors, but also by social workers, nurses, and mothers. One can't help think about the fact that Dickey listened to the mother of the child with sprue when she told him that the child did best when she didn't give him the treasured wheat that they had preserved. We can't predict what will happen, but some sensitive and open mind will get a clue from a clinical observation. I think on the experimental side, we are going to recognize, as in other slow viruses, that we will probably find it difficult to grow them and to see them, but in the end we will have to demonstrate their transmissability. I predict that if we can raise enough money, and get a colony of chimps, and instil into a jejunal fistula the ileostomy effluent of a patient who had Crohn's disease, we would convince ourselves after four or five years that the disease was transmissable.

Finally, I like to think that we will try to sort out the patients with inflammatory bowel disease, in whom we think the genetic mechanism has rendered them more or less susceptible, whatever the environmental triggering factor, so that we would tailor whatever drugs we have more appropriately. About a third of the patients with inflammatory bowel disease seem to be immunosuppressed at the time we see them. I think that we will tailor our drugs so that we will stimulate the immunosuppressed and depress the overstimulated.

Dr. Aufses: I think that if we look at the history of gastrointestinal diseases, we see some type of pattern. A disease is identified. It begins to increase in its incidence, either through an actual increase, or better recognition of it, or an increasing ability to diagnose it. It then plateaus, and then begins to decline. Certainly, that's been true of peptic ulcer disease. In this country, and actually worldwide, it reached its peak in 1945, and has been in continuous decline since. It is true of different carcinomas. Carcinoma of the colon is now on its way up, and carcinoma of the stomach seems to be declining. Dr. Lennard-Jones showed us a slide yesterday, where ulcerative colitis, which is now 106 years old, is perhaps beginning to decline. If I had to venture a guess, I would say that granulomatous disease, which has been on a marked increase in the northern parts of the world, will slowly plateau and then begin to decline. That will be followed by increases in its incidence in other parts of the world, where they don't see very much of it now.

I think we are going to find that the etiology of the disease is either a transmissable agent, or an environmental factor, acting on a susceptible host. As we begin to understand who the susceptible hosts are, we will be able to manipulate their DNA and redesign them in some way with some genetic engineering, so that they are no longer susceptible. I am more inclined to think, though, that we are going to find that it is a factor in our environment and then we will try to eliminate it.

In terms of where we can go experimentally, Mr. Alexander-Williams' concept that we are surgically basically treating scar tissue was a very intriguing one to me. I suspect, therefore, that the basic research endeavors in both of these diseases have to come from the basic scientists and those surgeons who are interested in the mechanisms involved in wound repair. We don't understand, for example, why ulcerative colitis heals and leaves an atrophied piece of bowel, and granulomatous disease heals and leaves a thickened piece of bowel. So we must learn how to control both inflammation and the growth of scar tissue. It seems to me that, at least in the granulomatous diseases, many of our problems would never occur if we could control formation of scar tissue.

Dr. Kern: I'd like to digress for a minute and ask John Alexander-Williams about his strictureplasties. This is an exciting idea, the idea of retaining bowel. I have agreed with you for many years that patients need their small intestine and we should remove as little of it as possible. You have presented us with a novel and I think exciting approach. I am sure that the surgeons in the audience are going to go home and take this message home with them. Is there anything you want to tell us that we should know about what should not be done, or any warnings or caveats, or special things we should know about this procedure?

Mr. Alexander-Williams: I think you shouldn't go overboard and believe it's what you should do in every case. Certainly, the primary terminal ileal Crohn's disease that needs surgery because of obstruction should still be treated in the conventional way. I'm sure that if you want to use this technique, you should start to do it on the quiescent multiple-stricture case. There are enough of those around. I've done it almost entirely on those, or people who are very short of gut. I think if you are doing it on a patient like the one I had this week, who was very short of gut, and very severely compromised, I think to do it under total parenteral nutrition and complete bowel rest is probably the answer—rather as we were saying yesterday with some of the surgery in Crohn's disease. If you have a two-week period of total bowel rest over the operation, I think it makes it a great deal safer. Providing you get rid of all the stenotic segments, and have no obstruction at all, you'll be all right. But it is very dangerous to do this and leave one of these strictureplasties proximal to another obstruction. It is quite difficult radiologically to be absolutely certain about distal obstruction. This is why I am trying to develop this sizing machine that you can put down the gut, because I think the great danger would be leaving multiple suture lines in diseased bowel when there was distal obstruction.

Dr. Kern: Thank you. My other question is, have you used this instrument you have just described to stretch strictures?

Mr. Alexander-Williams: No. But obviously we thought about doing this and I think it would be very nice to try this under operative control. What I have tried to do is to push my way through strictures, and it's very difficult. They are jolly tough. I think it would have to be something like a Tubbs dilator that you use for heart valves. It would have to be something that would expand. But we are actually trying it in the duodenum for duodenal stenosis, and I think if we do that nonoperatively, and it works, we might progress to Crohn's.

Additional Diagnostic Techniques?

Dr. Kern: Thank you. Now I'd like to move on to several specific questions, starting with Dr. Lennard-Jones. Do you foresee the development, or the need for additional diagnostic tools or techniques?

Dr. Lennard-Jones: Really it would be very nice to be able to diagnose inflammatory bowel disease by some test of the blood. I've taken some interest in the work of Witzig and his colleagues in Holland. They have found there is an excess of some organisms, called peptostreptococci, and new bacteria in Crohn's disease. Patients with Crohn's disease have an increased proportion of antibodies to these particular organisms in the blood. This isn't a specific test, but it's a useful idea. We know that patients with Crohn's disease have humoral antibodies to a wide range of *Escherichia coli* serotypes.

Now, I don't know whether these organisms said to have been described in Holland are at all specific to Crohn's. They feel perhaps that they are. But this is a useful and interesting approach. Apart from that I don't see any new techniques at the moment.

Mr. Alexander-Williams: As an extension to what I was saying about assessing the luminal diameter radiologically, I'd like a more effective method of assessing luminal diameter. I think it is quite important in our management of the disease and also in assessing the results of therapy. You don't always know if you have a stricture in Crohn's disease, you don't know how much is inflammatory edema and you don't know how much is fibrosis. I think if there was a good radiologic method of actually giving the precise diameter of the gut, you could then use that as a measurement of medical control. Also, it would help you if you were planning strictureplasties. I'd like my radiological colleagues to do that for me.

Dr. Janowitz: As you know, I'm no endoscopist, but I'd like to see the development of an instrument for viewing and biopsying further down the small bowel in the difficult problem of differential diagnosis of ileal lesions. All is not ileitis or regional enteritis that appears on an x-ray.

Dr. Aufses: One other specific question. Does anyone on the panel see the need for additional surgical techniques or surgical approaches? We've heard about one very exciting one.

Mr. Alexander-Williams: I would like to agree with what John has said about the development of continent nonstoma surgery. I would entirely agree with that, and it will be an important development in ulcerative colitis. I think the preservation of the anal sphincter for continence will be the ultimate goal. If you guys haven't found the cause of the disease and eliminated it in about twenty years, I think we shall no longer be giving people stomas. We will be using their own anus to give them continence.

Dr. Aufses: People have been trying this, as you know, for at least forty years. In recent years there has been a revival of interest. It is probably not quite the same operation today that it was forty years ago. Ravitch's procedure of anal ileostomy was a pioneer work but patients were dissatisfied because of diarrhea and perianal irritation. That operation had to fail. The operation as it's done today (and in this institution, they have been primarily done by Dr. Gelernt and Dr. Heimann) gives outstanding results. It's still only a small group, but a reasonable number of patients. As you saw from Dr. Gelernt's figures yesterday, the dissection is carried out inside the sphincters. The sphincters are all preserved. There is a good muscular tube. I believe, and perhaps Dr. Gelernt or Dr. Heimann can comment on this, that they've now done pressure studies at a considerably later date, and the pressure relationships in the ileum which has been transplanted into the rectal tube and anal canal responds just as a normal rectum does to distention and stimulation. So that once you are able to work within the sphincters and maintain the integrity of the sphincter mechanism you've got continence, and you've got what Mr. Alexander-Williams and Dr. Lennard-Jones would like to see.

Dr. Lennard-Jones: Yes, I've been watching this operation. My colleague, Adam Parks, at St. Marks Hospital, has been putting ileal reservoirs inside the muscular tube of the rectum and I see these patients and I think the outlook is very promising. I think the bugs of this operation are being worked out at the moment, but I look forward with enthusiasm to this.

Early Detection of Carcinoma

Dr. Kern: I am sure we all do. One other specific question concerns the early detection of carcinoma. To my mind, this is a major problem. Henry, would you like to begin the discussion here?

Dr. Janowitz: The current party line is to do biopsies at some fixed interval and ask our pathologist to tell us the early signs of carcinomatous antecedents, or carcinomatous transformation. We know that having locked them up in several rooms on several occasions, they have considerable difficulty in agreeing among themselves as to the criteria, although it is clear that as a result of these meetings, there is a consensus arising. I'd like to see more information on the question of the rate of growth of cancer of the colon in ulcerative colitis. I go on the assumption that since ordinary cancer of the colon doubles in two years, judged by missed cancers, or metastases, the same thing holds true for ulcerative colitis. I think what's needed now, if we can get it in some way, perhaps would be isolated in vitro studies of cell turnover, to learn something about the rate at which cancer develops in ulcerative colitis, which might then give me some more comfort at the rate at which I should keep my patients under surveillance. But, for the moment, I go by a rule of thumb.

Dr. Aufses: I think there is some very exciting work going on at Sloan-Kettering, primarily, by Drs. Deschner and Lipkin. Dr. Deschner's studies showing the migration of specific DNA-producing cells from the depths of the crypts up to the surface of the crypts is kind of an intriguing theme in its relation to the development of cancer. She is now almost able to predict a precancerous mucosa based upon her cell kinetic studies. She has been looking for inflammatory bowel disease specimens and we have given her a few. I don't know yet what the data show. I think this is a very exciting area to look at because I suspect, again, that at some time in the future dysplasia will not be the criterion that we use to decide when a patient has become precancerous, but that there will be some other far more sophisticated method, either biochemical or DNA-type studies, which will more readily identify the patients at risk.

Dr. Kern: John Lennard-Jones. Do you agree with that?

Dr. Lennard-Jones: I'm not sure that I do. I was very encouraged by this. Two or three colleagues of mine took biopsies and cultured them with radioactive thymidine. The interesting finding was that the increased rate of epithelial cell turnover was present in colitis in remission. One gets the picture of colitis in remission with this very rapid turnover of the epithelium all the time. I'd like just to put forward the provocative idea that the increased instance of cancer and colitis is just the ordinary incidence brought forward ten years.

Dr. Kern: Those are just the patients who get the cancers—the ones who are in remission, who have the very rapid turnover.

Dr. Lennard-Jones: That just means it is a dangerous disease.

Mr. Alexander-Williams: I think one quick look to the future is perhaps some improvement in knowing which areas to survey and which to biopsy. It is extremely difficult, from a practical point of view, to look at a patchy quiescent colon and predict which bits you ought to be biopsying. Malignant change only occurs in usually just one or two areas. Perhaps we shall shortly have better markers, better dyes maybe that are injected or sprayed, that will give us a better idea which parts we should be biopsying.

Dr. Kern: Dr. Janowitz, what is your present rule of thumb? How often do you recommend colonoscopy?

Dr. Janowitz: Once a year. After ten years.

Dr. Kern: You arrived at that interval because six months is too frequent and two years makes you uneasy. I just want to stress the fact that our state of the art here is very unsatisfactory. Now, I'd like to come to my favorite question, that I've prepared the panel for. That is: given unlimited resources, such as the Reagan defense budget, to apply toward the study of inflammatory bowel disease, how would you recommend that these resources be used? We'll start with Dr. Aufses.

How Would You Use an Unlimited Budget?

Dr. Aufses: I knew this question was coming from Fred's letter about three weeks ago. About all I could think of is that we tried that once in this country and we called it Nixon's war on cancer. We sure didn't get very far. I'm not really sure that Reagan's war on inflammatory bowel disease, or anybody else's war, is really going to pay off because it is quite clear that money alone does not solve any problem. I think that money is better spent in smaller quantities, but better directed. As I said earlier, I think the direction I would like to see this go, is in the biochemical approach to the processes which are responsible for the problems that we see in these diseases.

Dr. Janowitz: The modest steps that I think one might begin with, without invoking infinite space, time, and money, would be to exploit a few clues that have been popping around for a while. For example, on the therapeutic level, I would like to revert again to the question of the role of antibiotics in the treatment of Crohn's disease. There are enough sporadic anecdotes, and the experience of our predecessors, to suggest that we could, in a modest way, answer the question of whether the large amount of antibiotics that are currently being used in the underground treatment of Crohn's disease are worthwhile. Secondly, if we had more money and could attract more people, I think we ought to study the development of the cellular and humoral factors of the gut's defense. After all, this is the last frontier, and we need to know more about functional anatomy and the developmental immunology of the gut.

Dr. Alexander-Williams: I think I'd put up the surgical fees for operating on inflammatory bowel disease if I had infinite resources. Something that I have thought about, and have always been impressed by, is the geographical world epidemiological studies which show how rare this disease is, for instance, in the Mediterranean littoral. It is extremely uncommon. I feel that it is perhaps sunshine, citrus fruit, and siestas that are the essence of prevention of inflammatory bowel disease. If one had infinite resources, it would be a good idea to evoke the old concept that we had for tuberculosis, when we were as impotent in tuberculosis as we are in inflammatory bowel disease now. If you had infinite money you could rent a Caribbean island and turn it into a nudist colony where everybody ran around happily with their body image.

Dr. Lennard-Jones: I do take Dr. Aufses' point. I don't think that by pouring money into this we are going to solve the problem, but that rather more money would be very useful. I would put much more money into microbiology. I'm interested particularly in the bacterial flora, both in ulcerative colitis and Crohn's disease. I think that we need to get away from this business of getting the flora and then just naming it. We call it *Bacteroides*, or we call it *E. coli*, or whatever. I think this is holding us back at the moment. What we really need to know are what the bacteria do and what their antigens are. For example, we know very little about bacterial toxins and their effect in inflammatory bowel disease. We know very little about their metabolic effect. We have heard nothing these last few days about Rodgers' work, where he has shown that the metabolism of the epithelium of the colon is derived quite largely from nutrients in the lumen, particularly hydroxybutyric acid. This probably comes from bacterial action on substrates in the gut. That may be the link between diet and bacteria and inflammatory bowel disease. Because perhaps, as he suggests, this is why colitis involves the distal colon particularly, it's starved of its luminal metabolites, of its luminal nutrients. Now, this is a very important bit of work. So what we know is about bacterial metabolism. We need to know about bacterial toxins. We also need to know about bacterial antigens. One of the very exciting developments, I think, has been the relationship between the HLA types and their close relationships with certain bacterial antigens, particularly *Klebsiella*. This may be related to the reason that patients with inflammatory bowel disease, who are HLA-B27, get ankylosing spondylitis so much more easily. It's a reaction between bacteria coming from the gut and their own HLA antigen. This is a very good field for research. So I would put my money into microbiology. This is very expensive. It's very time-consuming work, and I don't think we're doing nearly enough of it. The transmission experiments we've heard about, and clearly they must go on.

I've been very interested in these experiments in the athymic mice. Leprosy has taught us something with the nine-banded armadillo. They have a specific animal there that is susceptible to leprosy bacillus. It is the only animal that is susceptible to leprosy bacillus in this particular way. We need a similar animal model. Perhaps the athymic mouse is that model.

Then, of course, I go back to my own favorite topic, therapeutic trials. I think in general, particularly for Crohn's disease, there have got to be multicenter trials. I've alluded to the need for a trial of bowel rest, elemental diets, total parenteral nutrition. At the moment, we in Britain are doing a trial on altering the amount of refined carbohydrate in the diet. We've got over 20 hospitals collaborating in this. All this takes money, and a lot of organization. I'd put money into this. Because if we don't know what causes the disease, at least we'd know more about how to treat it.

Dr. Kern: I gather that everyone on the panel seems to believe some sort of infectious agent or virus, or bacterial agent, or toxin perhaps, is primarily responsible for Crohn's disease in the susceptible host. Is that correct? In 1982, is that what everybody believes?

An Infectious Disease?

Dr. Janowitz: It is interesting that when we're in the presence of history: that when Dr. Bargen discussed Dr. Ginzburg's and Dr. Crohn's paper at the AMA just fifty years ago, he said in his last sentence: "I believe this is an infectious disease."

Dr. Kern: So, if everybody believes that, and if we had all the money that we need, why not go to every medical school in this country, and in England, France, Germany, and Switzerland, hire the best microbiologists and virologists and immunologists, and say: "Here's career support, all the money you need for equipment, and technical help, and so on. Find the cause of these diseases."

Dr. Janowitz: I think we have to inspire the bacteriologists and microbiologists to be interested in this disease.

Dr. Kern: They say they have projects that are more interesting.

Dr. Janowitz: They're frying their own fish.

Dr. Kern: Okay. Let's assume we could inspire them to do that by a session like this. What's wrong with that approach?

Dr. Janowitz: I don't think anything is wrong with it. I think Crohn's disease is too important to be left in the hands of gastroenterologists.

Dr. Kern: Would anybody else like to comment about this?

Dr. Lennard-Jones: I think it's a bit naive to believe that they would achieve anything. Would you find that if you locked bacteriologists in a room they'd ever achieve anything very much?

Dr. Kern: I'm just trying to be provocative. I've asked this question and I've presented this proposition to a number of microbiologists and virologists, and that's exactly what they said—"This would be looking for a needle in a haystack. And with all the money in the world, you couldn't persuade us to do it. We have our own projects that are intellectually more stimulating and this would be a waste of my career. Why should I do this?"

Dr. Janowitz: Well, don't lock them in a prison room. Lock them in a palace.

Dr. Kern: I don't believe that approach would work. I wish it would. Because as Dr. Aufses said, we tried to solve the problem of cancer by throwing money at it, without success. Well, to get on to the very last question, What should we do now and in the immediate future to get at the basic causes and treatment of these diseases?

What Should We Do Now?

Dr. Lennard-Jones: Certainly in Britain we do need more funding. There is no question about that. We are relatively starved of research money, and I think that we've got to raise funds. You've been more successful, I think, in doing that here in the States. I've told you how I would use a lot of those funds. I think, also, we've probably got to organize ourselves rather more, particularly for the combined clinical trials and so on. You've been organizing yourselves here with your collaborative studies on transmissibility, exchanging your material, exchanging results. We've had the collaborative studies of the pathologists looking at dysplasia in colitis. We need a lot more collaboration and organization. But I don't think organization is the answer. Because I have a shrewd suspicion that the answer to this problem will pop up in an unexpected place, just as Australia antigen popped up looking at aborigines in Australia, and nobody was looking for hepatitis B at all.

Mr. Alexander-Williams: Just speaking as a therapist, rather than wanting to find out more about the disease, I think we ought to look in the short term to doing less harm to patients than we are at the moment. If you look around your country and mine, much of the harm that's done to inflammatory bowel disease patients is done by physicians and surgeons who are not accustomed to looking after the disease. You still see absolute tragedies in the surgical management of inflammatory bowel disease. I think that in the immediate future, more centralization and patient education perhaps; educating patients to insist that their inflammatory bowel disease is treated by people who know what they are doing. I think that is particularly so in our country, and I think I would put some time and money into centralizing resources and educating patients to get the best possible treatment.

Dr. Kern: An excellent idea. Dr. Janowitz.

Dr. Janowitz: I certainly would underline and say amen to what Dr. Lennard-Jones has said about group activity and therapeutic trials. Then I would also place some wild bets. Subsidize not all the bacteriologists in the country, but try to persuade one or two outstanding younger persons, and endow them with time and space and money.

Dr. Aufses: Well, I think we shouldn't wait another fifty years before we have another conference like this, to bring together people like Lennard-Jones, Alexander-Williams, Fred Kern, Henry Janowitz, Leon Ginzburg, and all of the other people to discuss the new elements of what's going on. Because it seems to me progress is made when people like this get together frequently and fertilize each other with new ideas. So, I would vote for another one of these at an earlier date.

Dr. Kern: You've heard a great many, I think, very interesting and provocative and stimulating ideas presented here. I don't think I'll attempt to summarize. What you've heard has really been a summary. I would only emphasize that we do need more imaginative young investigators to go into this field, to try to help us understand it. We certainly need more money for more intelligent cooperative trials of what we are now doing. We need to follow up all of the clues that have been mentioned, from the epidemiologic to the biochemical, that have not yet been investigated. There's a great deal to be done and I hope that before we have the next such conference, regardless of when it is, a lot of these things will be done. I'd like to thank all of the speakers this morning, and thank our panel of clairvoyants, and to again thank the organizers of the conference and especially, to thank the audience.

Dr. Janowitz: Before you leave the podium, Fred, speaking for Arthur and myself, we want to thank you and John Lennard-Jones and John Alexander-Williams and the audience for making this a historic and profitable occasion. Thank you again.

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In Memoriam

JANE BAERWALD ARON

1914–1983

The passing of Jane Baerwald Aron interrupts but does not terminate a remarkable family tradition of service to Mount Sinai exceeding half a century. She was preceded by her mother Edith and her father Paul, towering figures both in the philanthropic community. Her husband Jack survives her to continue the Baerwald-Aron saga of devotion to Mount Sinai and munificence to it.

Under the aegis of mother Edith, who cofounded the Women's Auxiliary in 1916 and was its longtime president, Jane became a member in 1945 and president from 1966 to 1971. In 1964 Jane became a member of the Board of Trustees of the Hospital and, upon their formation, of the Boards of the Medical School and the Medical Center, in which capacities she served until she died.

In 1971 all three boards did themselves the signal honor of appointing Jane Aron as the first woman vice-chairman. She represented the Trustees to its Community Board, an important post requiring hard work, tact, and diplomacy. Jane displayed all of these. Among her unique contributions to the Hospital were her tireless activities as chairman of the Patient Services Committee and its three subcommittees, and ten years of herculean work for the Gift Shop. Tangential were her representing the Hospital on the United Hospital Fund and on its Program Committee, which was important to the larger community of the city and to the Hospital.

Two named professorships owe their existence to Aron-Baerwald giving, the Edith Baerwald Professorship of Community Medicine (Social Work), and the Jane B. and Jack R. Aron Professorship of Neoplastic Diseases of the Mount Sinai School of Medicine.

A tribute to Jane B. Aron as a person follows:

Jane B. Aron gave of her time, her effort, her commitment, her substance to Mount Sinai. She gave her experience, her counsel and enthusiasm. She gave her love. She gave herself.

She endowed the Institution with a standard of personal conduct that will make us all better as we strive to emulate it.

She invested in the Institution her concerns for mankind and the human condition, seeking to lift the yoke of disease and the burdens of being sick, by her efforts in social work, for nursing, by her concern for families and for patients.

She invested in the Institution through her concern for medicine and for medical research.

Often in the crucible of one's own crisis is forged metal of the finest temper. She faced her crisis with courage, commitment, self control and personal dignity. In the passages that were deep and difficult she looked unto the heights. During her illness she sometimes declined but did not complain.

It is my thesis that we should not be mourning the passage of another soul. Truly, we have been in the presence of a nobility of carriage that consecrates us all.

Rather, we should celebrate our great good fortune to have had this magnificent spirit among us.

Her influence will persist. She was loved, and is loved, and that love will continue to help us keep alive the things in which she believed.

James F. Holland, M.D.
January 19, 1983

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Joseph L. Goldstein, M.D. (*left*), and Michael S. Brown, M.D. (*second from right*), both professors of genetics at the University of Texas Southwestern Medical School, were the 1982 recipients of the Lita Annenberg Hazen Award for Excellence in Clinical Research for their work on the metabolism of cholesterol and atherosclerosis. With the winners at the reception in November 1982 were (*left to right*) Mrs. Hazen, Mount Sinai trustee; principal speaker James B. Wyngaarden, M.D., director of the National Institutes of Health and former member of the award committee; and Thomas C. Chalmers, M.D., president and dean, and chairman of the award committee.

Lita Annenberg Hazen Award 1982

Aaron B. Lerner, M.D., Ph.D., professor and chairman, Department of Dermatology, Yale University School of Medicine, the 1981 award recipient, made the following remarks at the November 9, 1982 presentation to Drs. Goldstein and Brown.

My colleagues in the biomedical community will share the pleasure of those assembled here when they learn that the Lita Annenberg Hazen Award for Excellence in Clinical Research has been given this year to Dr. Michael S. Brown and Dr. Joseph L. Goldstein.

These two young physician scientists have been among the first to demonstrate, at a molecular level, the involvement of receptors in the etiology of a particular disease. Studying patients with defects in the metabolism of cholesterol, they were able to unravel the complex processes whereby the intracellular levels of cholesterol regulate the activity of receptors for low-density lipoproteins.

Cholesterol is an important molecule in biological systems. It is essential for the formation of membranes of cells and it is used in the synthesis of several hormones and of bile acids. Yet if cholesterol, as part of the low-density lipoprotein (LDL), is elevated to high levels in the blood, early atherosclerosis and coronary heart disease follow. How is this balance between the essential and the harmful roles of cholesterol controlled? What defects are present in those people who belong to kinships with congenitally high levels of cholesterol in the blood? How does the increase or decrease of levels of cholesterol within cells feed back to regulate the activity of receptors for low density lipoprotein and its own synthesis?

Over the last ten years Dr. Goldstein and Dr. Brown have answered these questions through brilliant research. They asked the right questions and designed elegant experiments to answer them.

Recently they have advanced a hypothesis regarding the role of macrophages in the formation of atherosclerosis. Macrophages, which are part of the immune system, lack the normal receptors for LDL but instead express receptors that recognize a chemically altered form of LDL. It is possible that LDL is modified in vivo in some fashion to make it more atherogenic.

Doctors Brown and Goldstein have written extensively on many aspects of their subject. They have been active participants at numerous meetings and they have trained many MDs and PhDs. They have received several awards for their contributions. They will bring us up to date on their research later in the afternoon at Mount Sinai.

Now I want to spend a few minutes discussing another aspect of their success. People at Southwestern and those outside Texas say that the achievements of Goldstein and Brown are great in themselves but also represent the finest accomplishments, to date, from Southwestern.

I have always been interested in the development of new departments, research institutes, medical schools—and even new countries. How much time is required and what route must be followed before such institutions are able to post any major scientific advance? Sometimes such a young organization has the advantage that its new members look at a problem without traditional constraints. However, the new members are frequently distracted by the problem of getting things started and by the absence of a "critical mass" of colleagues.

The Nobel Prizes were first awarded in 1901 but it was not until 1943 that the prize for medicine and physiology was awarded to a native-born American, Edward Doisy, who received the prize for his work on vitamin K. The National Institutes of Health, reorganized in their current form, did not get going until 1950, with James Shannon first at the Heart and Lung Institute and later as director. Even with the combination of wise administration and lots of money, it wasn't until eighteen years later, in 1968, that Marshall Nirenberg at that institution won its first Nobel Prize.

From a great distance I've always followed the developments at Southwestern. In the mid-1940s, in the medicine outpatient clinics at the University of Minnesota I had an excellent teacher by the name of George Aagard. I'll skip Aagard's own interesting background and say only that in 1951 he became dean at Southwestern. A few years earlier, in the middle of World War II, Baylor Medical College had been enticed out of Dallas to Houston. Only a relatively unadventurous group of faculty was left behind, but some spirited citizens fought to keep a medical school in Dallas. Aagard was not the first dean but he was a revered one. In 1954 he left to become dean in Seattle. Aagard considers one of his major achievements to be the appointment of Donald Seldin as chairman of the Department of Medicine at Southwestern in 1952. To make Seldin chairman at age 32 was not easy. There was opposition from within, and Seldin's own household was packed to return to New Haven. Southwestern grew rapidly in size and quality. It took about twenty years for the base to be established for Brown and Goldstein to begin their research. Whether Brown and Goldstein consider this period to be long or short from an epidemiologic or statistical standpoint . . . I'll ask them in private later.

Whatever the answer, their research brings great credit to them and to their institution. We congratulate them both.

It is almost eleven months to the day that I was the recipient of this award. In addition to the obvious monetary benefits to me and to my laboratory there has been the bonus of getting to know Mrs. Hazen. Her interest and generosity in helping people through medical research are extraordinary. I have enjoyed her great personal charm, her wit, and her gift for independent thinking. It is good to see her again.

Aaron B. Lerner, M.D., Ph.D.

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FAME AVENUE, HANOVER, PA 17331 FOR THE MOUNT SINAI HOSPITAL BY THE COMMITTEE ON MEDICAL EDUCATION AND PUBLICATIONS (OW
EDITORIAL AND BUSINESS OFFICE: 10-35 ANNENBERG BUILDING, THE MOUNT SINAI HOSPITAL, ONE GUSTAVE L. LEVY PLACE, NEW YORK, NY 10
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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Pretreatment Marrow Cytogenetic Status: A Predictor of Response to Remission Induction Therapy in Acute Myelogenous Leukemia

MICHAEL S. CONJALKA, M.D., JANET CUTTNER, M.D., LAWRENCE WISNIEWSKI, PH.D., JUDITH D. GOLDBERG, SC.D., ARLENE REISMAN, A.B., M.P.H., ROSS ELLIOTT, A.B., ROBERT DESNICK, M.D., PH.D., JAMES F. HOLLAND, M.D., AND PAUL D. BERK, M.D.

Abstract

Seventy-nine of 161 previously untreated patients with acute myelogenous leukemia had cytogenetic studies performed on their bone marrow aspirates before remission induction treatment was begun. All patients received an identical induction regimen of cytosine arabinoside and daunorubicin. Patients whose pretreatment bone marrow cytogenetic studies were completely normal had a significantly higher complete remission rate and a lower rate of refractory leukemia than did patients whose pretreatment marrow yielded abnormal results. The clinical characteristics of the patients who had marrow cytogenetic studies were similar to those not so studied. Similarly, the clinical characteristics of the patients with normal and abnormal cytogenetic status did not differ. These data indicate that pretreatment marrow cytogenetic status is an important variable in predicting outcome of remission induction therapy in acute myelogenous leukemia.

Prior to the introduction of cytosine arabinoside, remission rates in acute myelogenous leukemia (AML) were low and remission duration brief. In 1968, cytosine arabinoside employed as a single agent was shown to induce hematologic remission in approximately 25% of AML patients (1). Furthermore, as a result of improved remission duration, the patients who attained remission lived longer than those who did not. In 1969, the combination of cytosine arabinoside and 6-thioguanine was demonstrated to produce remission in 40%–65% of AML patients (2, 3). At about the same time, the anthracycline antibiotics, daunorubicin and doxorubicin, were shown to be active agents in AML (4, 5). Since the late 1970s, combinations of cytosine arabinoside and daunorubicin, with and without 6-thioguanine, have been considered to be the best remission induction regimens for the treatment of acute myelogenous leukemia (6, 7).

Although current remission rates have improved over those of a decade ago, many patients with acute myelogenous leukemia still fail remission induction. In an attempt to determine which factors are associated with poor response to remission induction therapy, we examined the influence of pretreatment marrow cytogenetic status on the outcome of such treatment in acute myelogenous leukemia. This analysis suggests that the current remission induction strategy for AML is relatively ineffective in those AML patients with abnormal marrow cytogenetic status, as determined by standard direct cytogenetic studies.

Methods

The subjects in this series were the 161 patients with newly diagnosed acute myelogenous leu-

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This work was supported in part by Grants TM-AM07420 and CA-23102 from the National Institutes of Health and by a grant from the Interboro Leukemia Organization.

kemia who entered The Mount Sinai Hospital for remission induction chemotherapy between January 1974 and September 1980. Patients who had developed leukemia after a prior cancer or prior chemotherapy were excluded from this otherwise consecutive series.

In each patient the diagnosis of acute myelogenous leukemia was made after careful examination of marrow aspirates and blood smears, in all cases stained with Wright and Jenner Giemsa stains and, for patients entering the hospital in 1977 and later, with special cytochemical stains (8). For 79 of the 161 patients, a single pretreatment marrow aspirate was submitted for marrow cytogenetic analysis using quinacrine hydrochloride banding techniques. For the other 82 patients, pretreatment marrow cytogenetic studies were not performed because of limitations of laboratory space and personnel.

Marrow cytogenetic studies were performed via a modification of the technique of Tjio and Whang (9). An aliquot of the marrow aspirate was incubated in 5 ml of Media 1A (Gibco) containing 0.15 μg vinblastine sulfate (Lilly) for 1 hour at 37 degrees. The cells were then exposed to a 0.4% sodium citrate-potassium chloride hypotonic solution for 10 minutes, fixed in three changes of 3:1 methanol/acetic acid, dropped on wet slides, and allowed to air dry. Fifteen to 25 metaphases were routinely counted and analyzed at the microscope. Karyotypes were prepared from at least three to five representative metaphases stained with quinacrine hydrochloride.

The presence of two or more metaphases with an identical structural anomaly, two or more metaphases with an identical extra chromosome, or three or more metaphases with an identical missing chromosome were the criteria used for identifying abnormal chromosomal subpopulations (10–12). For the leukemia to be considered cytogenetically normal, there had to be at least 5 analyzable metaphases in the sample. Specimens which yielded fewer than five analyzable mitotic figures were classified as unsuccessful karyotypes. Specimens which did not appear completely normal but did not meet the specific criteria for cytogenetic abnormalities as proposed by conventions of the International Workshops on Chromosomes in Leukemia (10–12) were tabulated separately.

Describing marrow cytogenetic status as first proposed by Sakurai and Sandberg (13), patients whose marrow yielded only normal metaphases were classified as NN patients, those whose marrow contained both normal and abnormal metaphases were classified as NA patients, and patients whose marrow yielded exclusively abnormal metaphases were classified as AA patients. All marrow cytogenetic studies were interpreted without knowledge of the patients' courses and outcomes.

All patients received identical initial remission induction therapy: cytosine arabinoside (Ara-C) 100 mg/M^2 per day for 7 days by continuous intravenous infusion and daunorubicin 45 mg/M^2 as a single intravenous injection on days 1, 2, and 3 (7 + 3). On day 15 of the induction course each patient underwent a second marrow aspirate. If there was evidence of persistent leukemia at this time or any subsequent time during remission induction, a second course of chemotherapy consisting of 5 days of cytosine arabinoside and 2 days of daunorubicin was given (5 + 2). Patients were intensively supported with multiple antibiotics and human blood products as needed throughout their remission induction course (14, 15).

The outcome of remission induction therapy was classified in four categories: achievement of complete remission after (a) one or (b) two courses of chemotherapy; (c) died during the remission induction period; or (d) survived the remission induction period only to have the marrow repopulate with leukemic cells (16, 17), classified as having refractory leukemia (RL).

The presenting characteristics of patients who had cytogenetic studies and patients who did not have those studies were compared using methods of descriptive statistics, chi-square, and *t* tests to assess whether the group with cytogenetic studies was representative of all the patients in this series. Similar methods were used to compare the presenting characteristics of the NN and NA/AA patients to determine whether any factors other than cytogenetic status were associated with occurrence of remission in these patients. Remission rates were compared in those groups using chi-square tests and Mantel-Haenszel summary chi-square tests to adjust for other potential confounding factors.

Results

Of the 161 newly diagnosed AML patients in this series, 102 patients achieved complete remission after one or two courses of remission induction therapy. Of those not achieving remission, 38 patients died of complications of infection or bleeding during the remission induction period, 3 patients chose not to receive a second course of chemotherapy and left the hospital after 7 + 3 with evidence of residual leukemia, and 18 patients survived two courses of remission induction therapy only to be left with refractory leukemia (Figure 1). Thus, for this series of acute myelogenous leukemia patients, the complete remission rate was 63%, the fatal complication rate during remission induction was 24%, and the rate of refractory leukemia after 2 courses of induction therapy was 11%.

The presenting characteristics of the 79 patients with pretreatment marrow cytogenetic studies and the remaining 82 patients did not differ with respect to age at presentation, initial white blood cell count, initial platelet count, and initial hemoglobin levels (Table I). However, 67% of the patients with marrow cytogenetic studies were male compared to only 48% among those without such studies ($\chi^2_1 = 6.3$, $p = 0.02$).

Sixty-one of the 79 pretreatment marrow aspirates had a readily interpretable cytogenetic result, with an average of 21.5 (SEM = 3.0) analyzable metaphases per specimen. Of these, 38 patients were NN (cases 1 through 38), 11 patients were NA (cases 39 through 49), and 12 patients were AA (cases 50 through 61). The marrow cytogenetic abnormalities observed in the NA/AA patients are listed in Table II. The presenting clinical characteristics of the NN and the NA/AA patients did not differ significantly with respect to age at presentation, sex distribution, initial white blood cell count, initial hemoglobin levels, or initial platelet count (Table III).

The 66% complete remission rate for the NN patients is significantly higher than the 30% complete remission rate for the NA/AA patients ($\chi^2_1 = 7.18$, $p < 0.01$) (Table IV). When remission rates are compared for NN versus NA/AA patients, the rates tend to decrease with age in each group. After adjustment for age, however, the remission rate of the NN patients is still significantly greater than for the NA/AA patients (Mantel-Haenszel $\chi^2_1 = 5.4$, $p = 0.02$). Among the NA/AA patients, the 45% (5/11) complete remission rate for the NA patients was not significantly different from the 17% (2/12) complete remission rate of the AA patients ($\chi^2_1 = 2.3$, $p = 0.13$). However, for this analysis the numbers in each group are small. When the remission rates for the 61 patients with successful cytogenetic studies were compared, after adjustment for age, with the corresponding rates for the remaining 100 patients, these rates did not differ significantly (Mantel-Haenszel $\chi^2_1 = 3.38$, $p > .05$).

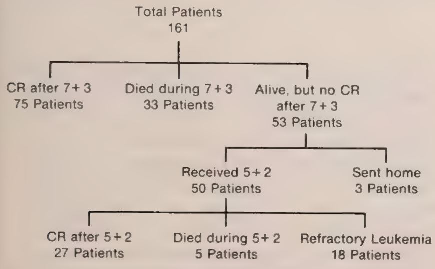

FIG. 1. Outcome of remission induction therapy for acute myelogenous leukemia at Mount Sinai Hospital, 1974–1980. CR: complete remission; 7 + 3 = cytosine arabinoside 7 days, daunorubicin 3 days; 5 + 2 = cytosine arabinoside 5 days, daunorubicin 2 days.

TABLE I
Pretreatment Characteristics of 161 AML Patients by Marrow Cytogenetic Status

Characteristic	Pretreatment Marrow Studies Not Performed No.	Pretreatment Marrow Studies Not Performed %	Pretreatment Marrow Studies Performed No.	Pretreatment Marrow Studies Performed %
Sex				
Male	39	47.6	53	67.1
Female	43	52.4	26	32.9
Age				
≤50 years	34	41.5	26	32.9
>50 years	48	58.5	53	67.1
WBC Count				
≤100,000/μl	66	80.5	67	84.8
>100,000/μl	16	19.5	12	15.2
Platelet Count				
≤20,000/μl	17	20.7	16	20.1
>20,000/μl	65	79.3	63	79.8
Hemoglobin				
≤8 gm%	30	36.6	23	29.1
>8 gm%	52	63.4	56	70.9
TOTAL	82	100.0	79	100.0

In examining causes of treatment failure (Table V), 3 of the NN patients (8%) were noted to have refractory leukemia. However, 2 of these 3 patients declined the second phase (5 + 2) of the remission induction regimen. Among the NA/AA patients, 9 (39%) were left with refractory leukemia after surviving both phases of the remission induction regimen. Thus, 23% (3/13) of the treatment failures in the NN group of patients were associated with RL compared to 56% (9/16) of the treatment failures in the NA/AA group ($\chi^2_1 = 3.25$, $p = 0.07$).

Cytogenetic studies on 18 of the 79 pretreatment marrow aspirates were classified as unsuccessful. Four of these specimens were not normal, yet could not be conclusively called abnormal according to the conventions of the International Workshops on Chromosomes in Leukemia (Table VI). Fourteen patients had cytogenetic studies which yielded four or fewer analyzable metaphases. Furthermore, these metaphases were

TABLE II

Pretreatment Marrow Cytogenetic Studies in NA/AA Patients

Patient No.	Age/ Sex	Marrow Karyotype*†	Metaphases # Normal/# Total	Cytogenetic Status (13)	Outcome of Remission Induction
39	79 M	46,XY/47,XY, +8	20/22	NA	D
40	65 F	46,XX/45,XX, complex	2/21	NA	CR
41	17 F	46,XX/47,XX, +8	6/20	NA	CR
42	62 F	46,XX/47,XX, +8	6/24	NA	CR
43	59 M	46,XY/47,XY, complex	12/24	NA	RL
44	68 M	46,XY/45,X	4/21	NA	RL
45	67 F	46,XX/46,XX, −7, +21	1/27	NA	D
46	67 M	46,XY/47,XY, +8	17/20	NA	CR
47	60 M	46,XY/47,XY, +8	17/20	NA	RL
48	31 M	46,XY/45,X, +13, −21	1/25	NA	CR
49	69 M	46,XY/46,XY,t(1;?)(q3;?)	2/5	NA	D
50	44 F	45,XX, complex	0/21	AA	RL
51	65 M	47,XY, +8	0/20	AA	RL
52	64 M	47,XY,r(5), + mar	0/5	AA	RL
53	76 M	44,XYY, complex	0/20	AA	RL
54	69 M	47,XY, +8	0/20	AA	RL
55	71/F	46,XX, −9, + mar	0/18	AA	D
56	64 M	47,XY, +8	0/17	AA	RL
57	60 M	47,XY, complex	0/19	AA	CR
58	65 F	48–63,X, +1, +11, +21, complex	0/11	AA	D
59	51 M	47,XY, complex	0/20	AA	D
60	48 M	47,XY, +8	0/15	AA	CR
61	55 M	45,XY, −9	0/18	AA	D

CR: complete remission; D: death during the remission induction period; RL: refractory leukemia.

* The term "complex" denotes multiple chromosomal rearrangements, "+ mar" denotes an extra chromosome which cannot be further identified, t( ) indicates a translocation between the chromosomes in parenthesis, r( ) indicates a ringed anomaly of the chromosomes in parenthesis, del( ) indicates deletion of part of chromosomal structure noted in parenthesis.

† The complete marrow karyotypes of patients with "complex" marrow karyotypes are as follows:

Patient 40: 46,XX/46,XX,t(3;11)(q29;q11)/46,XX, −14,t(3;11)(q29;q11) + r(14).
Patient 43: 46,XY/47,XY,-13, + mar, + mar.
Patient 50: 45,XX, −5, −6, −17, −21, + mar, + mar, + mar.
Patient 53: 44,XYY, −4, −19,t(9;17)(q3;q1),t(13;17)(q3;q1)t(17;17)
(p1;q1)/45,XYY, −4, −19,t(9;17)(q3;q1),t(13;17)(q3;q1),
t(17;17)(p1;q1), + mar.
Patient 57: 47,XY, −5, −11, + t(11;11)(p1;q1),t(18;20)(q1;p1), +21, + mar.
Patient 58: The abnormal cell line most frequently observed had the following karyotype:

50,X,t(4;X)(p1;p1), +1, +12, +21, + mar, + mar.

In some cells the chromosome number ranged from 48 to 63. This variation appears to be due to loss or gain of chromosomes in the cells of the 50,X line.

Patient 59: 47,XY,del(3)(p2),t(3;?)(q2;?), + mar.

generally of poor quality and, therefore, banding studies were not carried out. Nine (64%) of these latter patients achieved complete remission (Table VII).

Discussion

Previous investigators have recognized the poor therapeutic response of AML patients with abnormal cytogenetic status (13, 18–23). However, in these prior studies many patients were treated only with single agents, and other patients were treated with protocols which did not include an anthracycline. In addition, in some of the previous studies marrow cytogenetic status was obtained only after commencement of therapy, and patients often required multiple marrow aspirates for adequate cytogenetic studies.

The present study was conducted in a large group of AML patients, all treated with the same remission induction protocol at a single institution. It confirms that, even with a modern anthracycline-containing remission induction protocol, AML patients with major cytogenetic abnormalities in pretreatment marrow have a lower complete remission rate than corresponding patients who have cytogenetically normal marrow,

TABLE III

Characteristics of AML Patients by Result of Marrow Cytogenetic Status

Characteristic	NN No.	NN %	NA No.	NA %
Sex				
Male	23	60.5	16	69.6
Female	15	39.5	7	30.4
Age				
≤50 years	11	29.0	4	17.4
>50 years	27	71.0	19	82.6
WBC Count				
≤100,000/μl	30	78.9	22	95.7
>100,000/μl	8	21.1	1	4.3
Platelet Count				
≤20,000/μl	5	13.2	7	30.4
>20,000/μl	33	86.8	16	69.6
Hemoglobin				
≤8 gm%	12	31.6	6	26.1
>8 gm%	26	68.4	17	73.9
TOTAL	38	100.0	23	100.0

as observed in standard direct chromosomal preparations. Since our original report (24), two other groups working independently have reported similar results (25, 26).

Thus all studies which have examined the effect of marrow karyotype on the outcome of remission induction therapy for AML show that patients with abnormal marrow cytogenetic studies have lower complete remission rates than AML patients with normal marrow cytogenetic studies. Since successful outcome of remission induction is a necessary prerequisite for prolonged survival in this disease, AML patients with normal marrow cytogenetic studies, as a group, will survive longer than those with abnormal marrow cytogenetic studies.

Prior studies had not correlated the causes of treatment failure with marrow cytogenetic studies. In our series, the majority of failures oc-

TABLE IV

Outcome of Remission Induction Therapy as a Function of Marrow Cytogenetic Status and Age at Presentation

Age	NN* No. of Patients	NN* % CR	NA/AA† No. of Patients	NA/AA† % CR
≤30 years	4	75.0	2	100.0
31–50 years	7	85.7	2	50.0
51–60 years	12	66.7	5	20.0
>60 years	15	53.3	14	21.4
TOTAL	38	65.8	23	30.4

* Only normal metaphases in pretreatment marrow studies.

† Normal and abnormal, or all abnormal, metaphases in pretreatment marrow studies.

TABLE V

Outcome of Remission Induction Therapy as a Function of Marrow Cytogenetic Status

Outcome	Marrow Cytogenetic Status NN*	Marrow Cytogenetic Status NA/AA†
Complete remission	25 (65.8%)	7 (30.4%)
Mortality during remission induction	10 (26.3%)	7 (30.4%)
Refractory leukemia (RL)	3 (7.9%)	9 (39.1%)
TOTAL	38	23

* Only normal metaphases in pretreatment marrow studies.

† Abnormal metaphases present in pretreatment marrow studies.

TABLE VI

Patients with Cytogenetic Preparations Inadequate for Precise Determination

Patient	Age/Sex	Comment	Outcome*
62	12/M	20 metaphases analyzed 19 metaphases 46,XY 1 metaphase has 46,XY,4q+	CR
63	50/M	17 metaphases analyzed 14 metaphases 46,XY 3 metaphases have an extra chromosome: 1 of these is 13, the other 2 are D group, but cannot be conclusively identified as 13	RL
64	46/M	18 metaphases analyzed 17 metaphases are 46,XY 1 metaphase contains an extra F group chromosome which cannot be further identified	D
65	34/M	21 metaphases analyzed 21 metaphases are 46,XY 4 metaphases contain ?t (22,Y)	D

* CR: complete remission; D: death during the remission induction period; RL: refractory leukemia.

TABLE VII

Patients with Cytogenetic Preparations Containing Less than 5 Analyzable Metaphases

Patient	Age/Sex	# Metaphases	Outcome*
66	53/M	3	CR
67	52/F	0	RL†
68	24/M	0	D
69	67/M	0	CR
70	14/F	3	CR
71	29/M	0	CR
72	71/M	0	CR
73	43/F	0	RL
74	65/M	4	D
75	59/M	0	CR
76	23/M	0	D
77	55/F	0	CR
78	13/M	2	CR
79	33/M	2	CR

* CR: complete remission; D: death during remission induction period; RL: refractory leukemia.

† Did not receive second course (5 + 2) of induction therapy.

curring in NA/AA patients were due to leukemia refractory to the remission induction regimen and not due to death from infection and bleeding during the remission induction period. These data are consistent with the hypothesis originally postulated by Sakurai and Sandberg (18) that AML patients with major cytogenetic abnormalities in their marrow do poorly because these patients lack a sufficient population of normal stem cells to repopulate the marrow after remission induction therapy.

Our results suggest that conventional pretreatment marrow cytogenetic examinations can prospectively identify an appreciable fraction of AML patients with a particularly poor prognosis in response to conventional chemotherapy. It is possible that refinements in cytogenetic techniques and analysis may further improve the predictive value of this type of investigation (27).

With remission induction protocols that are currently being used for AML, between 60% and 80% of patients now achieve complete remission. The remaining patients either die of infectious or bleeding complications during the aplastic phase of the induction period or survive the induction period with refractory leukemia. In a series of AML patients treated 10 years ago at another institution with a different remission induction regimen, 9% of patients had refractory leukemia after Ara-C and 6-thioguanine (3). In our series, 11% of our patients had leukemia refractory to two courses of Ara-C and daunorubicin. Thus, it appears that the present anthracycline-containing remission induction regimen for AML has not decreased the rate of refractory leukemia from that of a decade ago. This may not be totally unexpected, since the strategy of every remission induction regimen employed over the last 10 years has been by necessity the same. Lacking drugs which are selectively toxic to leukemic cells, the goal has been to render the patient's marrow clinically aplastic and support the patient through the period of pancytopenia, in the hope that the marrow will repopulate with normal hematopoietic elements (28). This strategy fails when either (a) antibiotic and blood product support of the patient is not successful or (b) normal stem cells are unable to repopulate the marrow.

To further improve remission induction rates for AML, not only will support have to be improved for all patients, but new strategies for the treatment of AML patients with marrow cytogenetic abnormalities will have to be developed. These new therapeutic strategies should be applied not only to newly diagnosed AML patients who have major cytogenetic abnormalities in their marrow, but also to those patients who develop AML after previous hematopoietic disorders or previous cytotoxic therapy. These latter patients represent a population with a high incidence of marrow cytogenetic abnormalities, in which current remission induction therapy is largely ineffective (29, 30).

Acknowledgments

We wish to thank Ms. Natalie Flynn for her assistance in the preparation of this manuscript.

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Submitted for publication September 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Beneficial Effect of a Soy Flour Diet in Chronic Pancreatitis

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Abstract

The effect of a soy flour diet on secretin-pancreozymin and test-meal-stimulated pancreatic secretion was investigated in patients with chronic pancreatitis. Thirty grams of raw soy flour administered three times daily for one month resulted in a significant increase of enzyme secretion in response to Lundh test meal and to synthetic secretin and cholecystokinin-octapeptide (CCK-OP) stimulation. The functional capacity of pancreatic enzyme secretion remained elevated for at least three months after treatment. Symptoms of nearly all the patients ameliorated during and after treatment. The beneficial effect of the soy flour diet was attributed to the trophic effect of endogenous CCK released by a duodenopancreatic feedback mechanism.

The trophic effect of raw soybean diet is well established in chicks and rats (1–4). It causes hypertrophy and hyperplasia of the pancreas (5, 6), increasing the functional capacity of the total gland but not the individual acinar cells, as verified by secretin and cholecystokinin stimulation in anesthetized rats (7).

The trophic effect of a long-term soy flour diet on the human pancreas has not yet been studied. We published some preliminary data in a short report (8).

The present paper presents the effect of a soy flour diet on human pancreatic secretion stimulated by a test meal and by secretin and cholecystokinin-octapeptide (CCK-OP) to verify its usefulness in treatment of chronic pancreatitis.

Methods

The study was performed in 34 patients with chronic pancreatitis (15 women and 19 men; mean age 44.2 ± 2.16 in the women and 43.7 ± 2.31 years in the men. The duration of the complaint was more than 1 year (mean, 3.9 ± 0.45 years). Impaired glucose tolerance was observed in 11 patients, manifest diabetes in 1, and a hypoglycemic tendency in 1.

Prior to the study, 15 of the 34 participants were consuming more than 50 gm/day of alcohol, but they stopped drinking at least three months before investigation. Seven patients had undergone an operation on the biliary tract years before the study but thorough radiological examinations revealed no retained stones or microlithiasis. In two cases a fusion anomaly of the pancreas was demonstrated as a possible etiological factor (9). No definite cause of disease was detected in 10 cases.

Diagnostic criteria. The preliminary diagnosis was based on the typical history of chronic pancreatitis and on simple screening, either the starch tolerance test (10) or the lipiodol test (11), or both. In 7 participants an operation, in 8 participants endoscopic wirsungographic findings prior to the study had verified morphologic changes of the pancreas. Three participants had manifest steatorrhoea (7%-27%). The 34 cases were classified by exocrine function as mild disease (15 cases), moderate (15 cases), or severe (4 cases). After about a three-month period of dietetic treatment (including strict abstinence from alcohol) without relapse, pancreatic function was checked again by screening tests and exocrine pancreatic insufficiency was verified by secretin-pancreozymin or Lundh test, or both. The secretin-pancreozymin or the Lundh test was repeated after another three-month period. The original classification proved to be stable during the two 3-month periods.

Secretin-pancreozymin test. After simultaneous intubation of the stomach and the duodenum with a double-lumen Balzer tube, duodenal and gastric contents were aspirated in 10-

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min fractions with an electric pump. The basal fraction was discarded, and 125 ng/kg synthetic secretin (obtained as a generous gift from Prof. E. Wünsch) was given intravenously, and duodenal juice was collected for 30 min. Then a submaximal dose (50 ng/kg) of CCK-OP (research to be published) synthesized by our peptide team (12) was given and the duodenal content was aspirated for 50 min. The samples were put immediately in ice and examined within 4 hours. The volume was measured to the nearest 1.0 ml. Trypsin activity was estimated spectrophotometrically with α-N-benzoyl-D-L-arginine p-nitroanilide-HCl (BAPNA, Sigma) as substrate (13), lipase by a pH stat method with Sigma lipase substrate (14), and amylase with Phadebas® amylase test (Pharmacia AB, Uppsala, Sweden). In the postsecretin samples, bicarbonate concentration was measured with back-titration to pH 5 (13). Very rarely during the postsecretin phase some biliary reflux occurred; the figures on loss of duodenal volume were corrected using estimates of trypsin in the gastric aspirate.

Lundh test. Our modified, "quantitative" Lundh test (15, 16) was reported previously (17). Using as a control the secretin-pancreozymin (S-P) test, the Lundh test was performed in 14 of the 34 cases by the same intubation, 30 min after the control test. In the other 20 cases, only the Lundh test was made. In a prior study comparing the two tests (18), we found no differences in pancreatic responses when the S-P test preceded the Lundh test and when it did not.

Calculations. Mean activity of the 10-min periods and cumulative enzyme output were calculated for all enzymes. Activity and output were expressed also as percent change from start of treatment, taking that earlier value as 100%. Overall mean relative values (the sum of percent changes divided by 3) were also calculated to measure changes in total capacity of enzyme secretion (17). The results were statistically evaluated by Student's *t*-test for paired values or by Wilcoxon test.

Treatment. Natural soy flour (Rákosvölgye Co., Budapest) was administered for one month three times daily, 15 min before each meal in dosage of 30 gm in 250 ml of water. No other therapy was given during this period. Two days after the last administration of soy flour, secretin-pancreozymin or Lundh test, or both, were performed as a control for changes in the exocrine function of the pancreas. The Lundh test was administered to 19 participants after three months. At these control examinations detailed inquiries revealed the course of symptoms during and after the treatment as compared to the three-month pretreatment period.

Results

Only those patients who did not heal spontaneously during the pretreatment period were selected for the study. There was no substantial change in the overall mean relative values of repeated Lundh tests (Fig. 1).

Of the 34 participants, 9 became symptom-free and the condition of 18 significantly ameliorated during the last weeks of the treatment. There was no change in 6 patients; in 1 participant postprandial bloating with diffuse abdominal pain became worse. Relapse of the disease, measured by elevated serum amylase activity, did not occur. In some patients who complained of obstipation before treatment, stools were normalized, but diarrhea was not observed.

All 34 participants were measured by Lundh test at the end of treatment. All parameters of the test improved (Table I); 8 cases achieved totally normal values. The increases in trypsin secretion were more pronounced than increases in lipase; the augmentation of amylase was similar to that of trypsin. The volume of duodenal juice was not significantly increased. Overall output measured by Lundh test (Fig. 1) improved in 28 cases, did not change in 4, and diminished in two cases (27% and 28%). Changes in overall enzyme activity were similar.

In 14 patients secretin-pancreozymin test was also performed before and after the treatment. The overall changes of the secretin-pancreozymin test

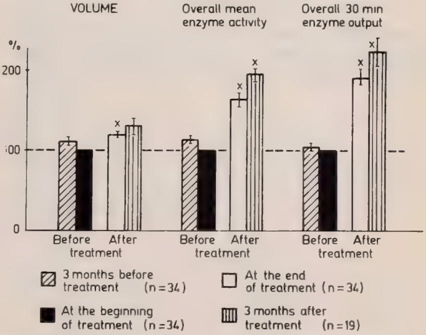

FIG. 1. Changes in Lundh test results before and after soy flour diet. Values at start of treatment were calculated from average enzyme activities and cumulative 30-min output of the three measured enzymes (trypsin, lipase, amylase). Relative changes of volume are also shown. Values are mean ± SE of the examined patients. *t* test for paired values, $p < 0.05$. X indicates significant difference from values at beginning of treatment.

TABLE I

Effect of Soy Flour Diet Measured by Lundh Test

		Trypsin		Lipase		Amylase	
	Volume ml/30 min	mean activity mIU/ml	cumulative output IU/30 min	mean activity IU/ml	cumulative output IU/30 min	mean activity IU/ml	cumulative output IU/30 min
Before	197.41	262.29	45.22	44.56	7644.40	56.36	10125.98
treatment	±14.781	±30.92	±5.42	±5.75	±1172.66	±8.34	±1498.48
After	209.53	413.30	82.49	49.76	9121.31	76.95	16414.14
treatment	±11.58	±49.66	±9.77	±5.47	±927.59	±11.42	±2533.31
Wilcoxon *p*	NS	<0.001	<0.0001	NS	<0.005	<0.005	<0.0001
% change from							
pretreatment	116.6	178.6	213.8	138.1	159.6	171.9	194.4
value (100%)	±6.36	±19.80	±24.03	±14.60	±18.27	±19.21	±22.33
Student *t p*	<0.05	<0.0001	<0.0001	<0.05	<0.005	<0.001	<0.0001

Values are mean ± SE, 34 patients.

and that of the Lundh test were similar in these patients (Fig. 2), but there was a significant (+142% and +55%) increase in the secretin-pancreozymin test values of the two patients in whom the result of Lundh test decreased. The augmentation of enzymes ran parallel (Table II). There were no substantial differences between the changes in the responses to secretin and to CCK-OP (data not shown).

In the 19 patients examined and tested 3 months after stopping the soy flour diet, the subjective and objective parameters remained at about the same level as at the end of treatment. In 8 some further amelioration occurred, in 2 patients pancreatic secretion did not change, in 6 patients it tended to return to and in 3 cases it relapsed to about the pretreatment level.

Discussion

The trophic effect of raw soybean meal is well documented in chicks (2, 3, 6) and rats (1, 4, 5) but not in pigs (19). Green and Lyman (20) hypothesized that in the basal state, intraduodenal trypsin inhibits cholecystokinin (CCK) release from mucosal CCK-cells (I-cells), and that blocking it by soybean trypsin inhibitor results in release of the stored CCK. Repeated CCK release evoked by the soybean diet may lead to hyperplasia of the pancreas (21). The concomittant increase in pancreatic secretion (1, 3, 4), particularly in response to secretin and cholecystokinin (7), might reflect the hypertrophy of the pancreas.

The CCK-mediated duodenopancreatic feedback regulation seems to exist in humans too (22-24). Diversion of biliopancreatic juice from the intestine (22) and intraduodenal soybean trypsin inhibitor (22, 24) results in hypersecretion by the pancreas. Natural soy flour stimulates pancreatic secretion more powerfully than heated flour (24), suggesting an additional CCK release which has been hypothesized to be involved in the trophic effect of soy flour diet in animals (20).

Indeed, the trophic effect of the soy flour diet seems to be significant also in humans, since in

TABLE II

Effect of Soy Flour Diet Measured by Secretin-Pancreozymin Test

			Trypsin		Lipase		Amylase	
	Volume ml/80 min	Maximum HCO_3 concentration mM/l	mean activity mIU/ml	cumulative output IU/80 min	mean activity IU/ml	cumulative output IU/80 min	mean activity IU/ml	cumulative output IU/80 min
Before	200.50	93.14	269.04	51.47	33.91	6530.87	82.42	15338.41
treatment	±14.75	±6.78	±37.16	±6.38	±6.81	±1166.89	±22.60	±4004.55
Wilcoxon *p*	NS	NS	NS	<0.05	NS	NS	NS	<0.05
After	216.71	92.79	306.63	67.68	36.75	8711.39	90.69	20579.45
treatment	±18.23	±5.87	±45.24	±8.14	±4.76	±1365.03	±19.86	±4411.93
% change from								
pretreatment	109.40	101.03	133.60	144.43	153.89	153.16	148.59	157.65
value (100%)	±6.89	±3.03	±18.41	±11.55	±23.13	±18.61	±34.27	±27.07
Student *t p*	NS	NS	NS	<0.005	<0.05	<0.05	NS	<0.05

Values are mean ± SE of 14 patients.

the series reported on here both the Lundh test and the secretin-pancreozymin responses were augmented after the treatment. These increases may be at least partially the consequence of an increased release of CCK due to the duodenopancreatic feedback mechanism. The trophic effect of CCK has been demonstrated in humans by secretory studies (17, 25). Morphologic or cytobiochemical evidence is naturally not available in humans.

Overall changes in enzyme secretion were similar to those which were found after CCK treatment (17), but the increase in trypsin levels was less pronounced in this series. The almost parallel augmentation of enzyme secretion after the soy flour diet may be the consequence of supplementary factors (5, 24) completing the CCK effect. CCK is known to stimulate trypsin synthesis more vigorously than amylase and lipase synthesis (26).

The increases in secretin-pancreozymin test findings were similar to those yielded by the Lundh test (Fig. 2), so we conclude that the simpler and cheaper Lundh test succesfully represents changes in the functional capacity of the pancreas. The test meal response demonstrates the physiologic situation during digestion. Intestinal factors may explain the decrease in Lundh test results in the two cases in which the secretin-pancreozymin test results increased at the same time. Maximum bicarbonate concentration did not increase; hence hyperplasia of ductal cells could not be proved.

The improvement in pancreatic function in our participants may be connected with amelioration of their complaints, but the subjective state of the participants did not always parallel the secretory changes. Loading of the gastrointestinal tract with large doses of soy flour sometimes caused bloating and a sense of fullness in sensitive patients. Yet lower doses of soy flour had a less trophic effect (8). Prolongation of the diet had no advantage. Some adaptation mechanism seems to be involved in the limitation of the trophic effect of a soy flour diet similar to the limits of CCK-OP treatment (17).

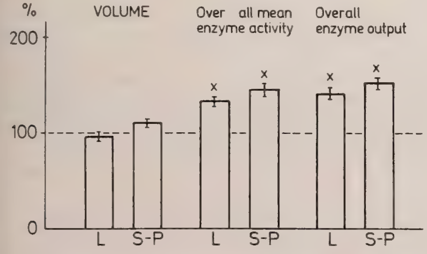

FIG. 2. Comparison of secretin-pancreozymin (S-P) and Lundh (L) test results in 14 patients. Overall relative values were calculated and statistically evaluated as in Fig. 1. Broken line represents pretreatment values. X indicates significant difference from pretreatment levels.

In recent animal studies by the Wormsley group (27, 28) a long-term (more than 90-week) soy flour diet acted as a cocarcinogen, even as a carcinogen, producing acinar cell adenomata and (rarely) carcinoma in the rats over two years old; but this malignant transformation of the hyperplastic acinar cells may occur only after such an extremely prolonged diet. Acinar cell carcinoma, however, is uncommon in humans (29, 30), even in regions where soybean is one of the prevalent constituents of the everyday diet.

In our participants pancreatic secretion remained elevated three months after the treatment (Fig. 1), so the soy flour diet seems to produce a definitive hyperplasia of the pancreas. The 3 relapsing patients may have returned to alcohol consumption or may have developed secondary biliary disorders. Similar factors may be supposed to have intervened in the nonresponding cases, whatever the effort prior to treatment to eliminate the causes of relapse.

The relative changes in the "mild disease," "moderate disease," and "severe chronic pancreatitis" groups were similar, showing that soy flour diet has a trophic effect in severe as well as mild or moderate chronic pancreatitis, but only in the mild and moderate cases were the absolute increases sufficient to allow abandoning substitution therapy. The increase in enzyme secretion may, however, ameliorate pancreatic responses to different meals in severe pancreatic insufficiency, since the participants' subjective evaluation of changes after treatment was positive in half of the cases.

In conclusion: the one-month soy flour diet seems to represent an effective treatment for cases of chronic pancreatitis with moderate pancreatic insufficiency. Its beneficial effect may be of long duration when the causes of relapse are successfully eliminated.

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Submitted for publication September 1982.

Editorial Comment. Dr. Pap and his associates present their data concerning a new approach to treating chronic pancreatitis. Their thesis is that the disease can be beneficially treated by administering a pancreatotrophic agent. The mechanism they propose is that soy bean trypsin inhibitor decreases duodenal pancreatic enzyme activity and by feedback mechanism induces pancreatic hypertrophy and hyperplasia. A therapy diametrically opposite in theory is also undergoing trial in Europe: the administration of pancreatic enzyme orally. The mechanism of this therapy would be to inhibit pancreatic enzyme secretion by a similar feedback mechanism. This inhibition of secretion would "splint the pancreas."

While the data are interesting, the protocol requires comment. First, the study did not include a control group, and, thus, the results are subject to bias and other errors. Second, no statement is made concerning the antiproteolytic activity of the soybean flour. Third, the case selection includes different varieties of the disease. Fourth, the use of starch tolerance and the Lundh test for diagnosis is open to criticism. Fifth, there is not statement concerning the clinical symptoms treated, hence it is difficult to evaluate just what "improvement" implies. A final caveat: there are some (Kenneth Wormsley, for example) who believe soy flour may be a cocarcinogen to the pancreas—it certainly is in the rodent. Further study is indicated.—*David A. Dreiling, M.D., Editor-in-Chief*

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Prostaglandin E_1 in Obstructive Peripheral Vascular Disease

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Abstract

A therapeutic trial of prostaglandin E_1 (PGE_1) was carried out with a patient who had severe obstructive peripheral vascular disease and an enlarging ischemic right-foot ulcer despite cessation of smoking and treatment with dypiridamol and bed rest. Angiography showed calf-artery occlusions and a pattern consistent with thromboangiitis obliterans. Because of recent encouraging reports in European trials on the use of intravenous PGE_1 and prostacyclin (PGI_2) for severe distal ischemia, prostaglandin E_1 was given by continuous intravenous infusion for 72 hours. The right-foot ulcer healed within two weeks and rest pain resolved completely after 48 hours. Serial treadmill evaluations have shown almost complete relief of intermittent claudication three months after treatment, enabling our patient to resume her nursing duties fulltime. Cessation of smoking remains a difficult but essential therapeutic modality, and very low dose aspirin (40 mg/day) may also help in sustaining the observed clinical improvements.

Therapy for obliterative peripheral vascular disease not amenable to reconstructive surgery has been very discouraging. In thromboangiitis obliterans (TAO), Buerger disease, multiple modes of therapy (sympathectomy, vasodilators, anticoagulants, antiplatelet agents) for disease that advances despite cessation of smoking have been discouraging; a 20% amputation rate ten years after onset of symptoms has been noted (1). Carlson and Ericksson (2) reported in 1973 the first trials of PGE_1 by intraarterial infusion in severe peripheral vascular disease; they obtained good objective results in three and relief of rest pain in all four cases. Again in 1976 Carlson and Olsson (3) reported rewarding results with PGE_1 infusion (this time intravenously) in eight cases without significant side effects. More recently, Szczeklik et al (4–6) and Pardy et al (7) have published their results in uncontrolled trials of PGI_2 and PGE_1 infusions for cases of severe peripheral vascular disease, including a significant number of cases with TAO. Although all these trials were uncontrolled, all the results were promising and long-lasting, and no significant side effects were encountered with intravenous infusion via a central venous catheter.

We report the case of a patient with obstructive peripheral vascular disease and an ischemic right-foot ulcer which progressed rapidly despite cessation of smoking and conservative treatment. Intravenous infusion of PGE_1 was followed by rapid healing of the ulcer, prompt resolution of rest pain, and long-lasting objective improvement in exercise tolerance without additional therapy except very low dose aspirin (40 mg/day), chosen for its potentially beneficial differential inhibition of prostacyclin synthesis and platelet thromboxane synthesis (8). Sustained cessation of smoking in our patient has also undoubtedly helped her clinical course.

Methods

A PGE_1 solution of 2.5 mg in 1000 cc of 5% dextrose in water, giving a concentration of 2.5 μg/ml, was prepared. Infusion via a central venous catheter was started at a dose rate of 0.007 μg/kg/min. Dose rate was increased gradually until the maximum recommended dose of 0.021 μg/kg/min was reached. All other medications were discontinued except for codeine 30 mg by

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mouth as required, which the patient took five times during the first 48 hours of the infusion period but did not require thereafter. A 72-hour continuous infusion was given. Dose rate was tapered in the last few hours of the infusion period as recommended in the protocol (Upjohn Research Protocol 2901 supplement) without any deleterious side effects or significant change in vital signs. Treadmill evaluations were performed at zero degrees of elevation and a speed of 2 mph. The case was monitored by representatives of the Upjohn Company and approved by the hospital Formulary Committee.

Case Report and Results

A 37-year-old white woman of Jewish ancestry was admitted with a six-month history of intermittent claudication of the right leg and two months of right-foot rest pain. She had a twelve-year history of Raynaud's phenomenon of the hands, 40 pack-years of cigarette smoking, but reported no history of diabetes mellitus, hypertension, thrombophlebitis, vasculitis, collagen vascular disease, dysphagia, use of birth control pills or any other drugs, or significant leg trauma. Treatment before admission with oral analgesics, vasodilators, and nonsteroid antiinflammatory agents provided only incomplete temporary relief of rest pain.

Physical examination on admission (including motor and sensory exam of all extremities) yielded normal results except in the vascular evaluation of both lower extremities. The right lower extremity showed absent dorsalis pedis and posterior tibial pulses, marked pallor on leg elevation, prominent dependent rubor of the distal right foot, and a 3 mm dark vesicle at the base of the third toe. The left lower extremity also showed absent dorsalis pedis and posterior tibial pulses and moderate pallor on elevation plus dependent rubor, but no lesions were present. Normal femoral and popliteal pulses were present in both legs. Doppler systolic pressure measurements at the ankles showed an ankle/arm ratio of 0.6 at the left dorsalis pedis and 0.0 on the right, where no signal was audible.

Results of laboratory studies on admission, including antinuclear antigen, qualitative latex, CBC and WBC differential, platelets, complete biochemical investigation, prothrombin time, urine analysis, and chest x-ray, were all normal except for an erythrocyte sedimentation rate of 46 mm/hr. A bilateral femoral arteriogram was performed (Figures 1 and 2), demonstrating diffuse bilateral peripheral arterial narrowing below

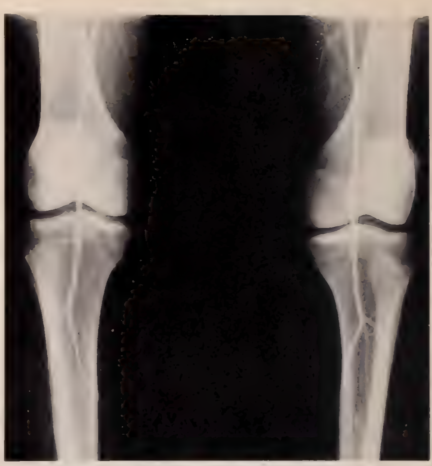

FIG. 1. Arteriogram of right and left femoral-popliteal artery systems demonstrating bilateral normal vessels above the popliteal trifurcation but severe diffuse narrowing occlusion of all distal arteries, right greater than left, plus tortuous collaterals.

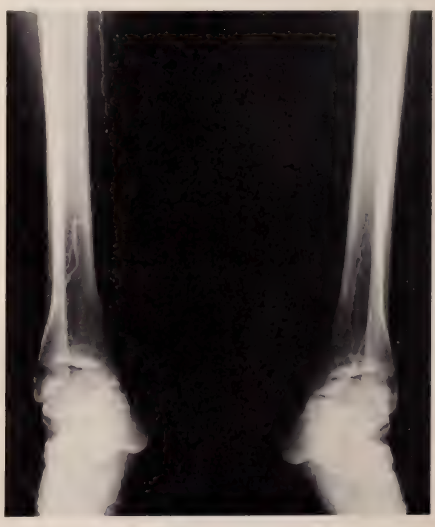

FIG. 2. Arteriogram of distal lower extremities showing diffuse bilateral arterial occlusions, again more pronounced in the right lower extremity.

the popliteal trifurcation, presence of tortuous collaterals, and completely normal proximal arteries. No change in arteriographic detail or pattern was noted after the intraarterial injection of papaverine. Comprehensive laboratory studies for possibly related diseases were unproductive (Table I). A diagnosis of obstructive peripheral vascular disease, consistent with TAO, was made and conservative treatment begun, i.e., cessation of smoking, bed rest, and dypiridamol 50 mg by mouth four times daily. Two weeks later she was readmitted for severe rest pain and development of a 10 mm by 12 mm necrotic ulceration in her right foot (Figure 3). Sympathectomy was considered but the patient rejected it.

TABLE I
Laboratory Test Results

ANA: negative
Qualitative latex: negative
VDRL: nonreactive
Direct Coombs: negative
HB ag: negative
Cold agglutinins: negative
GGTP: 14 mU/ml (norm, 7–23 mU/ml)
Amylase: 130 Dye U (norm, 200 Dye U)
Coagulation studies (PT, PTT, TT, fibrinogen FDP): within normal range
SPEP, IPEP, quantitative immunoglobulins: normal
Cryoglobulins: mildly positive in serum and plasma; normal IPEP on cryoglobulins
Bence Jones proteins in urine: negative
Lipoprotein profile: normal

A trial of intravenous prostaglandin E_1 was instituted under Upjohn Research Protocol 2901 and informed consent procedures. During the infusion, the patient reported gradual complete relief of rest pain and both feet were noted to be warmer. Side effects consisted only of temporary mild diffuse swelling and erythema of both hands and slight facial flushing. Postinfusion Doppler systolic pressure studies showed no significant change but ulcer healing (Figure 4) and sequential treadmill evaluations (Table II) demonstrated remarkable improvement. Elimination of rest pain and improvement in foot pallor and dependent rubor have persisted after six months of follow-up.

The patient has also been maintained on low-dose aspirin (40 mg/day) since the PGE_1 infusion, and has absolutely stopped smoking since the first admission. The arteriogram was not repeated, but it has been reported that arteriograms do not change significantly after prostaglandin infusion (4). Doppler systolic pressures were unchanged. Repeat CBC and white blood cell differential, platelet counts, erythrocyte sedimentation rate, biochemical investigation, urine analysis, and prothrombin time two months postinfusion were all normal.

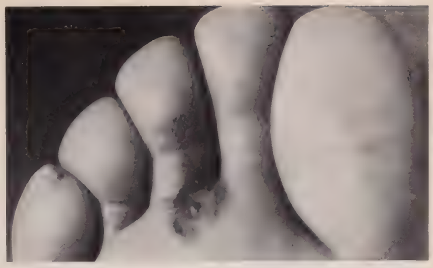

FIG. 3. Right-foot ulcer, preinfusion, after debridement of necrotic material, still showing necrotic base. Ulcer 1 × 1.2 cm; no signs of infection.

Discussion

Many conditions are associated with early or premature development of obstructive peripheral vascular disease, including diabetes mellitus, hypertension, lipid disorders, collagen vascular diseases, immune complex diseases, and certain drugs (amphetamines, polyvinyl chlorides, and ergot derivatives). No evidence was found for any of these conditions in our patient.

Thromboangiitis obliterans remains a poorly understood and controversial clinicopathological entity. Its greatest incidence is in Ashkenazic Jews, with a strong predilection for males in their 20s and 30s. No etiology has received general acceptance, but smoking aggravates this disease. Previous studies have suggested a thrombotic etiology, including a rise in adhesive platelet

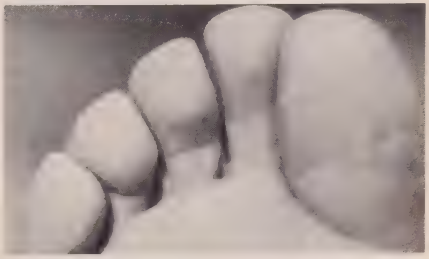

FIG. 4. Essentially complete healing of right-foot ulcer two weeks after infusion. The only topical care was to keep ulcer clean and protected.

counts associated with tobacco smoking (9). Raynaud's phenomenon and migratory thrombophlebitis may occur in up to 50% of patients. Intermittent claudication, rest pain, and digital ulcers are the same as in arteriosclerosis obliterans, but femoral artery disease is much less frequent and aortoiliac disease is very rare. Our patient is, except for being female, a close-to-classic case. Most of the other possible etiologies were excluded by comprehensive clinical evaluation and laboratory workup. Angiography was highly consistent with TAO and confirmed that reconstructive arterial surgery was not feasible.

TABLE II

*Sequential Treadmill Evaluations**

Period	Claudication Onset Time (min sec)	Degree/Site
Preinfusion	5:03	Absolute/right leg
Postinfusion	8:10	Absolute/right leg
1 month	5:40	Relative/right foot arch
2 months	15:00†	None

* All treadmill settings: elevation zero degrees, speed 2 mph.

† After 15 minutes without symptoms, examiner stopped test.

Treatment of the condition still tends to be mainly conservative, with appropriate emphasis on cessation of smoking, but the great difficulty in getting patients to stop smoking has led to a discouraging prognosis (high rate of amputation). Opinion is still divided on the usefulness of sympathectomy (1, 7, 10), which is probably advisable for patients who have disabling symptoms or face early amputation.

Prostaglandin E_1 is a potent vasodilator affecting mainly skin and muscle; it inhibits aggregation of neutrophils in vitro, but its platelet-inhibiting activity is much less than prostacyclin (7). The drug was originally given intraarterially because of the known rapid metabolism and elimination during passage through the lungs (2). Despite its rapid deactivation, prolonged relief of pain and increased skin temperature in ischemic areas has been reported with intravenous infusions through a central venous catheter (3). Prostacyclin (PGI_2), which is a very potent inhibitor of platelet aggregation as well as a vasodilator and is not removed by the lungs (but rapidly hydrolyzed in the circulation), has produced results equivalent to those reported with PGE_1 without appreciable side effects (4–7). Prostacyclin, in contrast to conventional antiplatelet agents, can inhibit platelet aggregation induced by all known stimuli. Platelet activity in vivo during prostacyclin infusion therapy has been shown to be suppressed but returns to normal shortly after termination of the infusion (6). The short-lasting antiplatelet and vasodilatory effects of PGI_2 and PGE_1 are in sharp contrast to the long-lasting clinical improvement observed, clearly a matter which deserves further research. Although the exact mechanism by which prostaglandins act is unclear, if the observed results are confirmed in carefully done controlled trials, PGE_1 or PGI_2 given intravenously may become the treatment of choice for surgically unamenable ischemic distal arteriopathy, especially thromboangiitis obliterans.

The beneficial effects of prostacyclin cannot be proven in our patient. Bed rest and strict discontinuation of smoking for 2 weeks had failed to improve symptoms and permitted the foot ulcer to progress. On the basis of several scientific studies and clinical case reports (2, 3, 4, 7), we were prompted to use prostacyclin in the hope of reversing the severe ischemia.

Our patient is now being maintained on 40 mg of aspirin per day. At this very low dose (but not in doses greater than 80 mg/day) prostacyclin synthesis is not inhibited, but platelet thromboxane synthesis is (8). If PGI_2 and thromboxane are important in the pathogenesis of thrombosis, then this low dose should be beneficial, while higher doses are unlikely to produce a favorable PGI_2-thromboxane balance. Prostacyclin synthesis is impaired in arteriosclerotic vessels and probably also in the vessels of persons with TAO, so keeping a favorable balance seems a logical choice.

A further implication in PGE_1 and PGI_2 studies and in our case is that healing of the ischemic lesion after surgical debridement is aided by an initial prostaglandin infusion because of the resultant improvement in tissue perfusion. Further studies are needed to determine the optimal dosage and infusion time, and when the drug should be given or repeated. There have been no reports to date of any delayed adverse effects with the use of these new and exciting agents, which are rapidly being found to be clinically useful in diverse conditions.

Finally, the importance of a detailed clinical and laboratory evaluation, including arteriography to rule out underlying treatable diseases and surgically amenable disease, should be emphasized. Cessation of smoking and avoidance of trauma and exposure to extremes of cold and heat are extremely important. The need for controlled therapeutic trials of these promising agents in the painful and frustrating diseases discussed here is urgent and essential.

Acknowledgments

The authors thank Dr. W. B. Martin of Upjohn Company for providing prostaglandin E_1 and Dr. H. Givre for his technical assistance.

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Submitted for publication May 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Prostacyclin: Effect on Pancreatic Lysosomes in Acute Experimental Pancreatitis in Dogs

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Abstract

Acute experimental pancreatitis (AEP) was induced in mongrel dogs by Elliott's method. Dogs were divided into 4 groups: I—AEP (n = 5), not treated; II—AEP (n = 6), treated with prostacyclin, dose 20 $ng/kg^{-1}/min^{-1}$ for 12 hrs; III—AEP (n = 5), treated 1 hr before induction of AEP and for 12 hrs as in group II; IV—control group (n = 6), healthy dogs. After 12 hrs the pancreata were removed and divided by degree of necrohemorrhagic changes into: A (mild), B (severe), and C (moderate) segments. The lysosomal enriched subfraction was isolated from the C segments at 15,000 × g for 20 min. The total (T) and free (F) activity of cathepsins and acid phosphatase was estimated and the value F/T, or relative free activity, was calculated as an index of lysosomal stability. In group I the relative free activity was higher than in the control group, especially in the B segments, suggesting labilization of pancreatic lysosomes during acute experimental pancreatitis. In group II and III the increase in relative free activity was limited in the A segments, suggesting a stabilizing effect of prostacyclin in mild necrotic changes. This effect was not supported in the pancreas parts classed as undergoing moderate and severe necrotic changes. Our results indicate prostacyclin has a protective effect against mild necrohemorrhagic changes during acute experimental pancreatitis, possibly by stabilization of pancreatic lysosomes.

The lysosomal hydrolases play an essential role in pancreatic degenerative processes (1). The release of acid phosphatase during autolysis of pancreatic tissue in vitro has been observed (2). Recently much data have been accumulated on the activation of pancreatic lysosomes during the course of acute experimental pancreatitis (3–6).

The release of lysosomal hydrolases seems to be an important factor in the pathogenesis of pancreatic necrosis because of their capacity in the digestion of cellular components (7) and activation of trypsinogen by cathepsins (8).

Manabe and Steer (4) reported that prostaglandin (PGE_2) diminishes cathepsin release in the pancreas and that mortality during diet-induced experimental pancreatitis in mice simultaneously decreases. However, Martin et al (9), after prolonged experiments, did not support these findings. Prostaglandins E_1 and E_2 inhibit the release of acid hydrolases from the lysosomal subfraction of the pancreas and other tissues (10). Such an effect is not documented for prostacyclin, but one may suspect that because of its activity in increasing c-AMP level (11), it is also the stabilizing agent. Moreover, prostacyclin (PGI_2) is effective in the improvement of microcirculation and disaggregation of platelet clots (12), in the abolition of leukocyte infiltration (13), and in inhibition of pancreatic (14) and gastric (15) secretion.

These properties of prostacyclin could be useful in the treatment of acute pancreatitis. On the other hand, some proinflammatory properties of this compound have been reported (13). Thus it is difficult to anticipate the final result of treatment of acute pancreatitis with prostacyclin.

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The study was partly supported by the Polish Ministry of Health and Social Welfare (problem MZ-III-C). Paper presented in part at the XIV European Pancreatic Club, September 1982, Essen.

The purpose of the work reported here was to evaluate prostacyclin protection in acute experimental pancreatitis in dogs, considering its effect on the activity of pancreatic lysosomal hydrolases and the stability of lysosomes in this organ.

Materials and Methods

The experiments were carried out on 22 mongrel dogs of both sexes weighing 12–16 kg, fed with a standard diet. The animals were fasted for 12 hrs before experiments, with free access to water. Dogs were subdivided into four groups as follows:

I. Dogs with AEP, untreated with any drugs (n = 5); only a supplementary intravenous saline infusion at a constant rate (2 ml/kg^{-1}/hr^{-1} for 12 hrs) was given.
II. Dogs with AEP (n = 6), treated with prostacyclin at the dose of 20 ng/kg^{-1}/min^{-1} for 12 hrs starting immediately after induction of pancreatitis. The volume of saline infusion was as in group I.
III. Dogs with AEP (n = 5), treated as in group II and in addition treated with the same rate of PGI_2 infusion 1 hr before the induction of pancreatitis.
IV. Control group, healthy dogs (n = 6).

The prostacyclin was a gift from Upjohn Co., Kalamazoo, Michigan, USA. The dose and the treatment methods were chosen according to studies in men (12).

Induction of Acute Pancreatitis. Pancreatitis was induced by the method of Elliott et al (16) with our slight modifications. The anesthesia was induced with intravenous injection of hexobarbital. After a sterile laparotomy and incision of duodenum the main pancreatic duct was cannulated with a metal cannula. A mixture of dog bile and trypsin was injected into the pancreatic duct under pressure exceeding 30 cm of water (measured manometrically during injection). The mixture was prepared from pooled vesicular bile from healthy dogs, collected postoperatively in sterile conditions. Samples of bile (10 ml) diluted with saline solution (1:1) were incubated with 12 mg of trypsin (Ferak, Berlin) at 37°C for 24 hr before the experiments. For 10 kg of animal body weight, 7 ml of the mixture was applied, and for every additional kg an extra 0.2 ml was added. All portions of the mixture after incubation were controlled microbiologically in agar cultures with negative results.

After 12 hr the dogs were killed by cardiac embolization with air to avoid the effect of other drugs on subcellular structures. As soon as possible samples of pancreatic tissue were taken from homogenization and for histological examination.

Homogenization. The pancreata were taken to glass vessels cooled with ice. The whole organs were dissected according to macroscopic appearance into segments A, B, and C. The segments were homogenized in 0.25 M sucrose, buffered with acetate buffer 0.005 M pH 5.0, with cooling in ice, using a motor-driven Potter-Elvejhem homogenizer equipped with a Teflon pestle, at 1500 rpm, 3 up and down strokes during 1 min. Whole homogenates from segments A and B were taken directly for enzymatic assays. The homogenate from segment C was centrifuged for the separation of lysosomal enriched subfraction.

Isolation of lysosomal enriched subfraction. The homogenate from segment C was centrifuged at 600 × g for 10 min in Janetzki's centrifuge K-24, with cooling to 4°C. The nuclear pellet was discarded and supernatant was centrifuged at 1000 × g for 10 min to sediment of zymogen granules subfraction, according to Hokin (17). The pellet was discarded and supernatant was centrifuged at 15,000 × g for 20 min to obtain the lysosomal enriched subfraction and supernatant.

The pellet was washed with cooled, buffered sucrose solution, the same solution used for homogenization, and was again centrifuged as before. The supernatants from the two last steps were mixed and designated as final supernatant. The pellet was gently, manually rehomogenized in Potter-Elvejhem homogenizer with Teflon pestle, using a suitable volume of buffered sucrose solution.

Enzymatic assays. In whole homogenate, in lysosomal enriched subfraction, and in supernatant the total and free activity of cathepsins and acid phosphatase were estimated by the method of Gianetto and de Duve (18), standardized in our laboratory: incubation time 10 min at 37°C, pH 5.0. The respective substrates were bovine hemoglobin (Sigma) and sodium β-glycerophosphate (BDH). The total activity was released using Triton X-100 (Rohm and Haas Co.) at concentration of 0.1% v/v in final incubation mixture (19). Enzymatic units: 1 U cathepsins = 1 μEq of thyrosine, 1 U of acid phosphatase = 1 mg of inorganic phosphorus released during 10 min incubation. The activities were expressed in units per gm of tissue or subfraction proteins estimated according to the method of Lowry et al (20) with bovine albumin (Pentrex) as a standard. The percentage ratio of free to total activity, or relative free activity, was accepted as an index of lysosomal stability.

Histological Examination. The specimens from segments A, B, and C were taken for routine hematoxylin and eosine examination, and for histoenzymatic reaction on acid phosphatase by Gomori's method as described by Pearse (21).

Statistical analysis of the results was by simple Student's *t* test.

Results

Gross Examination

In all animals with acute experimental pancreatitis, after 12 hrs poor general condition was observed. At autopsy severe hemorrhagic necrosis of the pancreas was invariably present, with focal necrosis of fat tissue in the neighborhood of the pancreas and serosanguineous fluid in the peritoneal cavity. In the pancreata three zones of changes could be optically distinguished (Fig. 1).

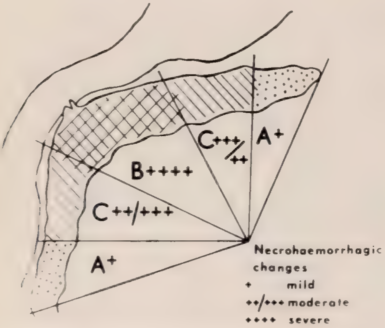

FIG. 1. Scheme of dissection of pancreata into segments A, B, and C on the basis of gross appearance.

On gross examination of segment B (severe changes) no difference between the untreated and the treated groups was found. However, in segments with moderate and mild inflammatory changes, the pancreata of animals from the treated groups seemed to be less changed.

Light Microscopy

The broad spectrum of changes from mild to severe necrosis of the gland could be seen in the majority of cases. We accepted the following scale for the systematic evaluation of histologic changes of pancreata, which roughly correspond to the results of gross examination.

Mild necrosis: The acini were dissected with interstitial edema containing numerous granulocytes and scattered erythrocytes. The acinar cells revealed a vacuolar degeneration; some of them had undergone coagulation necrosis. In some small venules the fresh vascular thromboses were present.

Moderate necrosis: Focal acinar necrosis and more advanced degeneration of acinar cells were observed. Edema, inflammatory infiltrate, and vascular thrombosis were more evident than in the "mild" group. Scattered interstitial hemorrhages were present.

Severe necrosis: There was confluent coagulative necrosis of entire lobules with numerous hemorrhagic foci. Marked acute inflammatory infiltrate was present. In scarce, relatively well preserved acini, the acinar cells showed advanced degenerative changes. Numerous capillary thrombi and thrombosis of greater vessels with almost complete obturation of the lumen were seen.

The incidence and severity of histologic changes in all groups are summarized in Table I. Thrombotic changes in vessels of pancreata in the treated and pretreated groups were less advanced and fewer than such changes in the untreated group (Figs. 2, 3).

Biochemical Assay

Whole Homogenates. The most important finding in segment A (mild inflammatory changes) was decrease of relative free activity of cathepsins in prostacyclin-treated and especially in the pretreated group in comparison to group I (Fig. 4). A similar trend emerged for the relative free activity of acid phosphatase (Fig. 5).

In segment B (severe inflammatory and necrotic changes) only the relative free activity of acid phosphatase evidenced a trend similar to that for segment A (Fig. 5). The protective effect of

TABLE I

Incidence of Pancreatic Necrosis

	A-Mild Change			C-Moderate Change			B-Severe Change		
Grade	I	II	III	I	II	III	I	II	III
0 (none)	0	0	0	0	0	0	0	0	0
1 (mild)	2	4	5	0	3	2	0	0	0
2 (moderate)	3	2	0	5	3	3	0	3	3
3 (severe)	0	0	0	0	0	0	5	3	2

I: untreated II: treated after induction III: treated before and during induction.

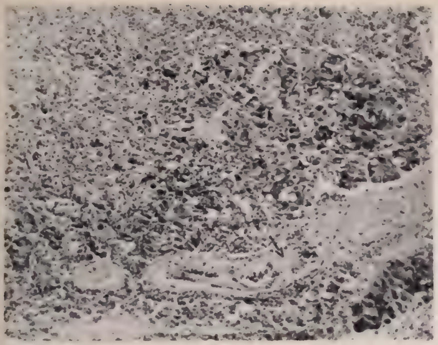

FIG. 2. Histologic picture of segment B, severe changes in pancreas, from untreated dog. Note thrombus (arrow) almost completely obstructing the vessel lumen (H + E ×100).

prostacyclin pretreatment on the relative free activity of cathepsins on segment A did not show up for segment B; in fact a trend to increase of this activity was observed in the prostacyclin-treated group (Fig. 4).

Lysosomal Enriched Subfraction and Supernatant. The total activity of enzymes in the lysosomal enriched subfraction roughly imitated the changes in whole homogenates. It is noteworthy that a surprising high activity of cathepsins was recorded for the prostacyclin pretreated group. The relative free activity (RFA) of both hydrolases was insignificantly lower in group II than in group I. In group III the RFA of acid phosphatase was similarly lower, but cathepsins remained unchanged. In the supernatant, the RFA of acid phosphatase was virtually the same in the treated and the untreated group, whereas the RFA of cathepsins showed a significant decrease in the groups with prostacyclin protection (Figs. 6, 7).

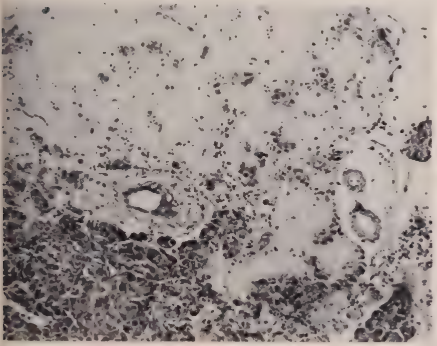

FIG. 3. Histologic picture of segment A, mild changes in pancreas, from group treated with PGI$_2$. Thrombotic changes in vessels are absent (H + E, ×100).

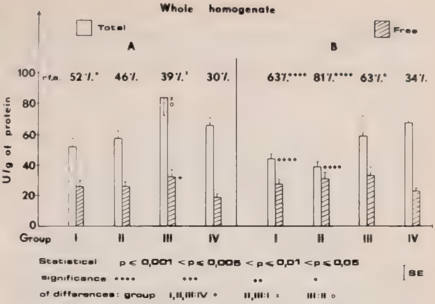

FIG. 4. Total, free, and relative free activity (%) of cathepsins in whole homogenate of segment A (mild changes) and B (severe changes), in all experimental groups.

Histoenzymatic Reaction on Acid Phosphatase

A variety of lysosomal changes along the entire pancreas stained for acid phosphatase were seen. In the areas of mild inflammatory change the stain was rather particulate. The acid phosphatase positive particles were enlarged in size and intensely stained without evident diffusion of their content (Fig. 8). The portions of pancreas evidencing moderate changes had diffuse enzymatic activity; however, large areas lost the enzymatic product (Fig. 9). In parts with severe necrohemorrhagic change it was impossible to evaluate any details of histoenzymatic reaction.

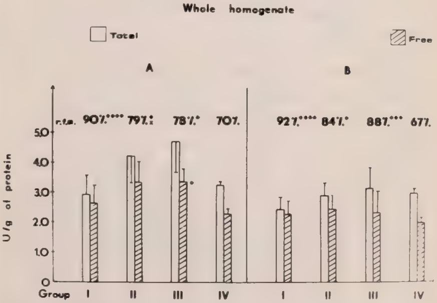

FIG. 5. Total, free, and relative free activity (%) of acid phosphatase in whole homogenate of segments A and B of pancreata in all experimental groups.

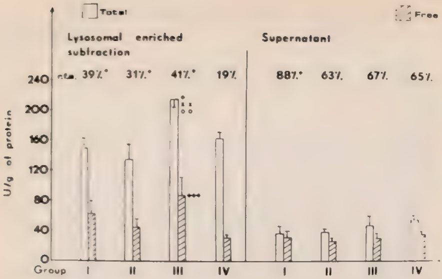

FIG. 6. Total, free, and relative free activity (%) of cathepsins in lysosomal enriched subfraction and supernatant of pancreas in all experimental groups.

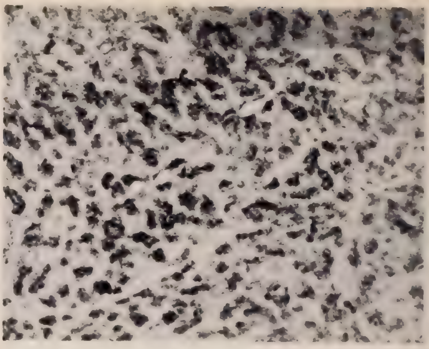

FIG. 8. Granular reaction on acid phosphatase in segment A, mild changes in pancreas, from group treated with prostacyclin.

Discussion

Our results showed an increase of relative free activity of lysosomal hydrolases in whole homogenate and lysosomal enriched subfraction of inflamed pancreas, suggesting the labilization of pancreatic lysosomes during acute experimental pancreatitis. The most advanced changes were observed in the portions of pancreatic tissue with severe necrohemorrhagic change. These findings are in agreement with our previous thesis (3), which has been supported by other authors (4–6).

In dogs with acute experimental pancreatitis pretreated or treated with prostacyclin, a reduction of relative free activity of cathepsins and acid phosphatase in the mildly inflamed portions of the pancreas was found. This finding suggests a protective effect of prostacyclin in less advanced acute pancreatitis. This result supports the stabilizing effect of prostaglandins on pancreatic lysosomes during diet-induced acute pancreatitis in mice reported by Manabe and Steer (4). However, in severely inflamed tissue with advanced necrotic and hemorrhagic changes, treatment with prostacyclin did not exert any evident protective effect. In the pretreated group, the relative free activity of cathepsins was also unchanged, indicating the absence of a protective effect of prostacyclin in severe necrosis.

The most advanced necrotic changes were observed in the areas directly infiltrated with bile during the induction of pancreatitis. Thus, it is likely that a harmful solution could reach the endoplasmic region of acinar cells by the endocytosis pathway described by Herzog and Reggio

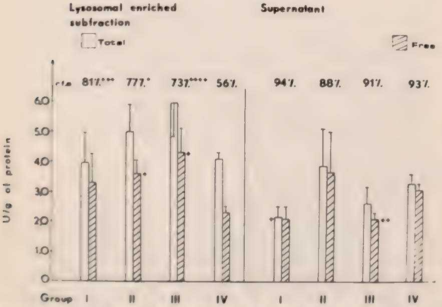

FIG. 7. Total, free, and relative free activity (%) of acid phosphatase in lysosomal enriched subfraction and supernatant of pancreas in all experimental groups.

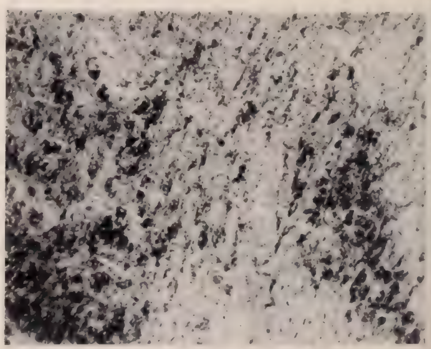

FIG. 9. The diffuse reaction on acid phosphatase in segment C, moderate changes in pancreas, from untreated group. Note loss of reaction product from large areas of tissue.

(22). In this case the "cytoprotective" effect of prostacyclin would simply be ineffective. Additionally, endogenous prostaglandin synthesis could be augmented following the hydrolysis of phospholipids by phospholipase A in necrotic fields (23) and could potentiate the proinflammatory effect of prostacyclin.

The effect of prostacyclin treatment on the lysosomal enriched subfraction from moderately inflamed portions of pancreas was slight and insignificant, but a considerable diminution of the relative free activity of cathepsins in the supernatant was observed, suggesting that the protective action on plasmatic sources of cathepsins could be the factor limiting the progressive lysis of acinar cells.

In pancreas parts with mild changes the histochemical reaction on acid phosphatase was granular and augmented, suggesting some adaptative changes of lysosomes directed toward the limitation of the harmful effect of noxious agents on the acinar cells. In parts with moderate changes, this defensive mechanism seems to be broken, and the reaction on acid phosphatase is diffuse. In some areas the product of enzymatic reaction is absent, suggesting that autolysis is almost complete. This last picture prevailed in the untreated group.

An extremely complicated situation arises during acute pancreatitis; different intensities of inflammatory change exist in one organ. Simultaneously the bioavailability of prostacyclin differs depending on disturbances in microcirculation. Additionally, the ratio of prostacyclin to the endogenous prostaglandin level seems to be different along the entire organ. Prostacyclin inhibits the leukocyte response 20 times more than does PGE_2 and is 5 times less effective than PGE_2 in edema production (13). Moreover, it is especially effective as a platelet clot disaggregating factor (11), preventing disseminated intravascular coagulopathy as a possible complication of acute pancreatitis (24). Therefore, in a considerable part of the inflamed pancreas the positive effects of prostacyclin could prevail and even prevent more advanced necrotic changes.

In prior works we have documented the stabilizing effect of prostacyclin on hepatic (25) and renal lysosomes (unpublished data) damaged during acute experimental pancreatitis in dogs. Moreover, we have reported the beneficial effect of PGI_2 on mitochondria of the liver depressed during the course of acute experimental pancreatitis in dogs (26).

From the data presented here we conclude that PGI_2 is an effective agent against acute experimental pancreatitis in dogs.

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Submitted for publication February 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Stress and Diseases of the Upper Gut
I. Stress and Liver Disease

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Abstract

The connection of stress with peptic ulcer and colon disease has long been recognized, but little has been said about the effect of stress on other organs of the upper gut (liver, pancreas, gallbladder). This, the first of three papers on that neglected topic, examines the connections between stress and liver disease. Many known stressors may cause liver disease, as manifested by the common biopsy finding of centrolobular necrosis or degeneration. Histologically, it is not possible to distinguish between etiological agents. In our review of the literature, the basis of these changes appears to be hypoxia or anoxia. Tissue hypooxygenation is therefore postulated as one of the common pathways by which these changes are induced.

Stress and illness is a much discussed topic today (1). The cardiologist engages in long dissertations on stress and heart disease (2, 3). Gastroenterologists have, for years, written about stress and peptic ulcer disease (4–8) as well as stress and colon disease (9–12), but have had little to say about the other organs of the upper gut. This then is the first of three papers dealing with the relation of stress to diseases of these other organs—liver, pancreas, and gall bladder.

Stress ulcers of the gastroduodenum have been described following burns, intracranial injuries, shock, trauma, sepsis, myocardial infarction, surgery, and multiple organ pathology (6). The same stressors have proven to cause liver disease, the microscopic picture of which is centrolobular necrosis or degeneration.

Kew et al reported this pathology following heat stroke (13). Cohen and Kaplan showed central hepatic necrosis in liver biopsies in cases of left-sided heart failure (14). Ritt et al stated that "The clinical findings of severe liver disease, clinical course, laboratory data, and pathology in the liver are indistinguishable in our patients regardless of whether the etiology is halothane necrosis, infectious or serum hepatitis" (15). They quoted Cook and Sherlock, who observed a similar overlap of findings in patients with hepatic necrosis due to hepatitis and various drugs.

Babior and Davidson reported on a study of 57 patients with massive liver-cell necrosis postoperatively; the etiology was thought to be shock or congestive heart failure (16). Fulminant hepatic failure secondary to congestive heart failure was also described by Kisloff and Schaffer (17).

Das, Nussbaum, and Leff's paper on hepatic function as related to acute myocardial infarction pointed out that hemodynamic changes may play an important role in the genesis of altered liver function (18) and, significantly, attributed these hemodynamic changes to three important physiological stresses: severe pain, tissue damage, and circulatory disturbances in association with severe psychological stress. These stresses resulted in low oxygen tension and constriction of the mesenteric vessels (splanchnic and hepatic blood flow), and these changes in turn were attributed to a decrease in systolic volume, cardiac output, and cardiac index with an increase in peripheral resistance due to an increase in endogenous norepinephrine.

Clarke (19), quoting Moon, emphasized that centrolobular necrosis followed trauma, postoperative shock, crush syndrome, burns, infections, blackwater fever, high altitude flying, and experimental shock. Clarke attributed liver changes in cardiac infarction to the acute anoxia of the shock resulting in a progressive fall in oxygen tension in the blood transversing the sinusoids.

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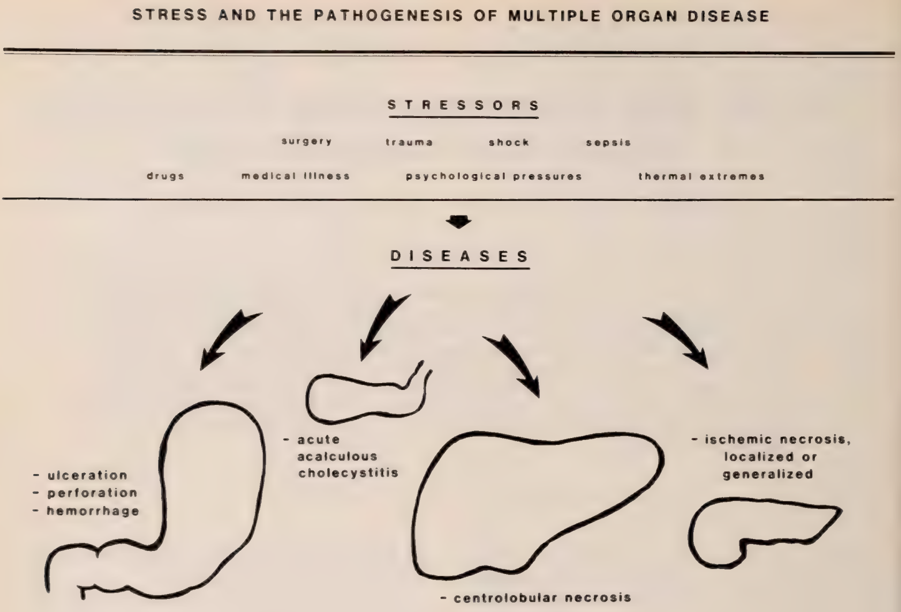
STRESS AND THE PATHOGENESIS OF MULTIPLE ORGAN DISEASE
STRESSORS
surgery
trauma
shock
sepsis
drugs
medical illness
psychological pressures
thermal extremes
DISEASES
- ulceration
- perforation
- hemorrhage
- acute acalculous cholecystitis
- centrolobular necrosis
- ischemic necrosis, localized or generalized

Shoemaker et al (20) described similar changes in the liver in hemorrhagic shock following gastrointestinal bleeding, postoperative gastric surgery, prostatic surgery, gunshot wounds of the abdomen, myocardial infarctions, aortic aneurysm surgery, intracranial hemorrhage, and pulmonary emboli. Again, anoxia of the hepatic cells was reported as the cause of centrolubular necrosis.

Nunes, Blaisdell, and Margretten (21) suggested that the central necrosis was due to the stress of surgery and anesthesia. The necrosis was not a specific lesion of shock because it also occurs in uremia, thyrotoxicosis, severe anemia, and exposure to various toxins such as carbon tetrachloride. The centrolobular necrosis was not due to the toxic effect of any definite agent but was probably due to the relative or absolute anoxia of the liver (21).

Ellenberg and Osserman (22) emphasized the role of shock in the production of central liver cell necrosis. They noted: "It is quite obvious that the pathology is a manifestation of anoxemia," and added that "central cell necrosis is not a lesion specific for shock, but is probably the end result of any prolonged vasospasm, anoxia, and acute circulatory insufficiency" (22).

Bynum et al reported severe cases of ischemic hepatitis misdiagnosed as viral hepatitis. Inadequate perfusion due to hypovolemia and hypoxia was the culprit (23). Refsum's description of centrolobular necrosis associated with pulmonary insufficiency also pointed out that hypoxia and hypercapnia were responsible (24).

The American literature contains little about the effects of emotional stress and liver disease. *Dorland's Medical Dictionary* (24th ed.) does record, under "jaundice," "emotional jaundice, jaundice resulting from deep emotion, such as great anxiety." In the Italian literature, Lambusta cited a case of acute yellow atrophy of the liver and psychoemotional stress (25), which he thought played a role, albeit secondary to viral disease. On the other hand, nonmedical references to the association of stress and liver disorder abound. Thus, Chaucer in his *Canterbury Tales,* ca 1386, wrote: "The Pardoner had her as yellow as wax" (26). Shakespeare expressed the relationship in "She pined in thought and with a green and yellow melancoly, she sat like patience on a monument, smiling at grief" (26). One quotation—from J. J. Connington's *No Past Is Dead* (1942)—serves to note how several apposite associations ("lily-liver" and fear, "yellow" as a sign of what psychologists refer to as the flight stage) have passed from common observation into the language of metaphor in English: "he's chicken-hearted and lily-livered with a yellow streak through the rest of his anatomy" (26). However, it took Hirose et al to document experimentally the influence of emotional stress on liver blood flow (27). Using colloid Au^{198}, they observed a decrease in the rate of disappearance of the colloid in patients with liver disease, the decrease correlating with the severity and chronicity of the disease. In normal persons subjected to anxiety and fear under hypnosis, the rate of disappearance of the colloid also decreased—and the decrease was more marked in known neurotic patients. Hirose et al concluded that it was possible that emotional stress played a role in causing liver disease or inducing a predisposition to it, and noted that "the psychosomatic concept may also be applied to some extent in the diagnosis and the treatment of liver disease" (27).

We conclude that one of the primary effects of various stressors on the liver is hemodynamic. Vasospasm with the resulting hypoperfusion compromises the hepatic cells in the centrolobular region.

Acknowledgments

The authors are very grateful to the librarian of the Touro Infirmary, Patricia J. Greenfield, and her assistant, Mary E. Hess.

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Submitted for publication November 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 3, May—June, 1983
Printed in U.S.A.

The Epidermal Poroma

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Abstract

"Epidermal poroma" is my term for a common benign intraepidermal germ cell proliferation of adnexal origin. It is recommended that this term replace the terms identifying three supposedly different adnexal neoplasms, namely hidroacanthoma simplex, trichilemmoma, and inverted follicular keratosis, the histopathology of which seems based on dubious grounds. In an analysis of 75 cases, these adnexal germ-cell proliferations seemed to differentiate toward sebaceous duct structures. The essential basic histologic hallmarks of the epidermal poroma are acanthosis, usually a component of verrucous epidermal hyperplasia; focal basaloid cell proliferation; and papillary dermal angioplasia. Seborrheic keratoses and other nonadnexal epidermal nevi represent benign intraepidermal germ cell proliferations of nonadnexal origin. Histologic criteria differentiating epidermal poroma from seborrheic keratosis, verruca vulgaris, hypertrophic actinic keratosis, and incipient-stage keratocarcinoma are detailed. Not infrequently, mixed lesions having the histologic features of both an epidermal poroma and a seborrheic keratosis were encountered.

Cutaneous adnexal oncology remains a fascinating but bewildering field of dermatopathology. Benign adnexal neoplasms restricted either to the dermis or the subcutaneous tissue and involving both epidermis and dermis are well recognized (1,2). The former include the numerous tumors of pilosebaceous and sweat-gland origin and the latter include eccrine poroma, syringocystadenoma papilliferum, pilar sheath acanthoma, trichofolliculoma, some sebaceous adenomas, and rare organoid nevi of sweat-gland and pilosebaceous origin. I have realized for some time that there exists an exceedingly common benign cutaneous neoplasm of adnexal origin which does not seem to have been clearly delineated histologically. Because of histologic similarities, this lesion is frequently misdiagnosed, most frequently as seborrheic keratosis or wart, less often as hypertrophic actinic keratosis or incipient-stage keratocarcinoma. Furthermore, because of a wide range of histologic patterns, this lesion has been considered to represent different entities, including hidroacanthoma simplex, trichilemmoma, and inverted follicular keratosis (1, 2), which are believed to be pathogenetically related to the sweat duct, outer root sheath (trichilemma), and hair follicle, respectively. My purpose is to present a single unified concept of the pathogenesis of this lesion, to propose a simple yet clear and meaningful name for it, and to detail its histopathology in comparison with the histopathology of the other dermatoses for which it is often mistaken.

Materials and Methods

Skin biopsies of 75 consecutive benign cutaneous adnexal neoplasms were reviewed from the files of the Skin and Mucous Membrane Biopsy Laboratory, Tenafly, NJ. Clinically, they were generally verrucous, erythematous, or skin-colored papules of several months' to many years' duration and were diagnosed as either warts or actinic or seborrheic keratoses. Approximately 85% of the lesions were located on the head, and most often involved the nose, cheek, eyelid, forehead, perioral area, and chin; an appreciable number also occurred on the trunk and extremities. The lesions occurred in patients in the second to the tenth decade, the majority of cases occurring in the patients' sixth or seventh decade. Staining techniques employed included hematoxylin and eosin (H & E), periodic acid-Schiff with and without diastase, alcian blue (pH 4.5 and 0.5), and the Feulgen reaction for deoxyribonucleic acid.

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Results

It became readily apparent that all 75 of the benign adnexal neoplasms studied represent germ-cell proliferations which differentiate in the direction of poral structures. Therefore, I have chosen to call them epidermal poromas. I believe this is an ideal and appropriate term because "epidermal" indicates confinement to the epidermis and "poroma" alludes to the poral structure of the adnexa which these germ-cell proliferations seemingly attempt to form.

All the epidermal poromas shared several histologic features. Their histopathologic features are compared in Table I with the features of seborrheic keratoses, verrucae vulgares, hypertrophic actinic keratoses, and incipient-stage keratocarcinomas. In the ensuing paragraphs, the term "other lesions" refers only to the five lesions listed in Table I. Although some authorities may con-

TABLE I

Comparative Histopathologic Features of Epidermal Poroma

	Epidermal Poroma	Seborrheic Keratosis	Verruca Vulgaris	Hypertrophic Actinic Keratosis	Incipient-Stage Keratocarcinoma
Papillomatosis	− to +	− to +	+	+	+
Hyperkeratosis	− to +	− to +	+	+	+
Epidermal dipping	− to +	− to +	− to +	− to +	− to +
Acanthosis	+	+	+	+	+
Parakeratosis	− to +	− to +	+	+	− to +
Hypergranulosis	− to +	− to +	+	− to +	+
Nuclear inclusions	−	−	+	−	−
Keratohyaline granules	N to G	N to L	L to G	N to L	N to L
Basaloid cell proliferation	+	− to +	−	−	−
Cytoplasmic vacuolization	− to +	− to +	+	− to +	− to +
Cytoplasmic glycogen	+	+	+	+	+
Mucin	− to +	− to +	−	− to +	−
Thickened basement membrane zone	− to +	−	−	−	−
Mature sebaceous cells	− to +	−	−	−	−
Premature keratinization	− to +	− to +	−	− to +	+
Hyaline bodies	−	− to +	−	− to +	−
Anaplastic dyskeratosis	−	− to +	−	− to +	−
Keratinocytic anaplasia	−	− to +	−	+	−
Suprabasilar clefts with acantholytic cells	−	−	−	− to +	−
Squamous eddies	− to +	− to +	R	R	R
Horn cysts	− to +	− to +	R	R	R
Hyaline lining of horn cysts	− to +	R	R	R	R
Pseudocysts with horn	− to +	− to +	− to +	− to +	− to +
Papillary dermal angioplasia	+	−	+	−	−
Subepidermal capillary ectasia	+	− to +	+	− to +	+

+ = present R = rare L = large
− = absent N = normal size G = giant

sider Winer's dilated pore to represent an epidermal poroma since it is an adnexal epidermal tumor which forms a poral structure, I consider that this lesion represents a malformation and not a neoplasia because it is a relatively stable localized excess of mature skin constituents (2). The epidermal poroma, however, is a neoplasia because it is an unstable localized excess of immature and maturing skin constituents.

Figures 1–10 detail the histopathology of the epidermal poroma. Except for a relatively small percentage of epidermal poromas and some flat and acanthotic seborrheic keratoses, all lesions showed varying degrees of papillomatosis and hyperkeratosis. Acanthosis was universally present

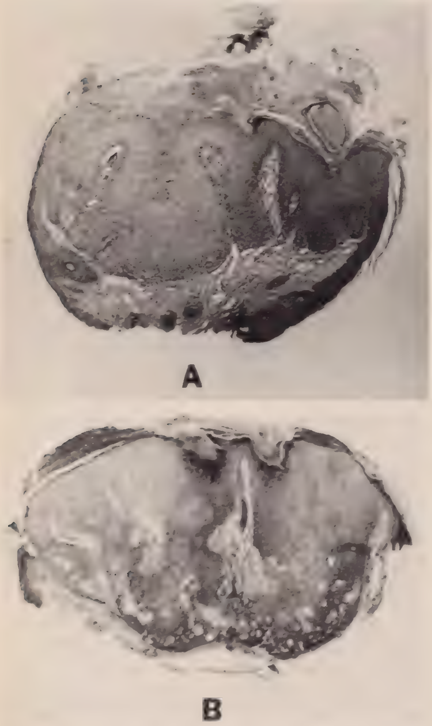

FIG. 1. Scanning view of two typical epidermal poromas showing verrucous epidermal hyperplasia in association with dipping of acanthotic epidermis well below skin surface, focal basaloid cell proliferation, and papillary dermal angioplasia. Premature keratinization, present in both lesions, is prominent in A. B shows clusters of sebaceous cells, horn cysts, and squamous eddies at base. Note absence of basal cell destruction (H & E ×20).

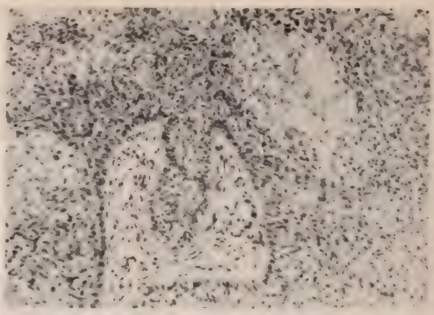

FIG. 2. Base of epidermal poroma demonstrating papillary dermal angioplasia, prominent thickened basement membrane zone below well-defined palisaded and focally vacuolated basal layer and almost imperceptible blending of focally vacuolated basaloid cells, large prematurely keratinized squamous cells and squamous eddies (H & E ×100).

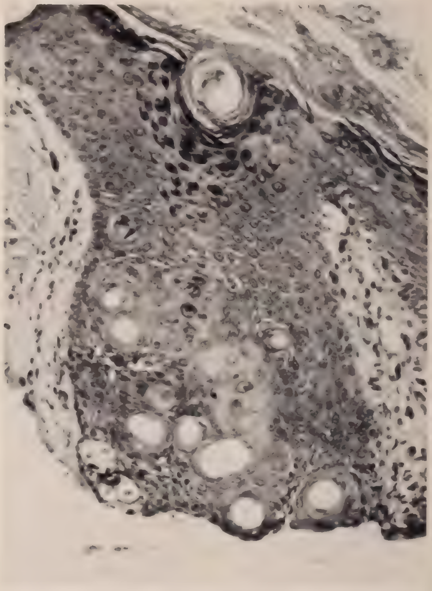

FIG. 3. Portion of epidermal poroma showing apparent progressive formation of poral structure starting at base with haphazard arrangement of sebaceous cells, focally vacuolated basaloid cells and squamous eddies which form concentric laminations about and merge with horn cysts containing little or no keratin with hyaline lining and no granular layer, progressing upward to surface with formation of pore plugged with keratin and lined by keratinized stratified squamous epithelium with markedly thickened granular layer containing giant round keratohyaline granules (H & E ×100).

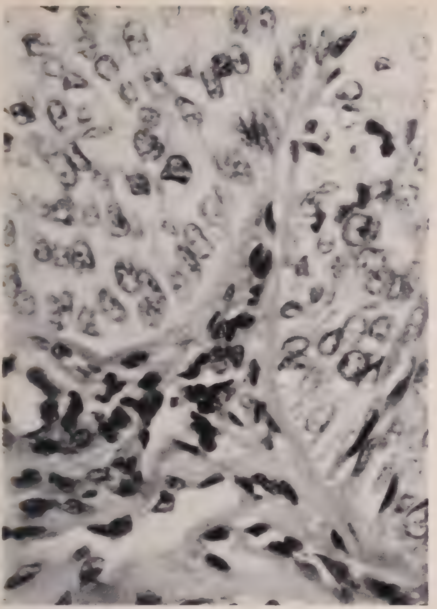

FIG. 4. Base of epidermal poroma detailing papillary dermal angioplasia, thickened basement membrane zone, well-defined palisaded and vacuolated basal layer, and marked vacuolization of basaloid cells above (H & E ×400).

in all lesions, generally occurring in association with papillomatosis, hyperkeratosis, and parakeratosis (verrucous epidermal hyperplasia). Dipping of the acanthotic epidermis ("epidermal dipping") well below the level of the skin surface was a conspicuous feature of most but not all epidermal poromas (Fig. 1), but was also observed within many of the other lesions. An occasional epidermal poroma with epidermal dipping had a large central keratin-filled cystic depression. When epidermal dipping was absent, these lesions were either polypoid papules or nodules, sometimes attached by a narrow pedicle, or verrucous or flat papules or plaques. Parakeratosis was always observed in varying amounts in the verrucae vulgares and hypertrophic actinic keratoses but was not a consistent finding in the other three lesions. The verrucae vulgares and the incipient-stage keratocarcinomas always showed foci of hypergranulosis, which were only variably present within the other three lesions. Intranuclear inclusion bodies, when present, could be demonstrated only within the granular and horny layers of the verruca vulgaris with confirmation by the Feulgen reaction. When present, the keratohyaline granules often assumed gigantic sizes within the epidermal poroma and the verruca vulgaris and frequently appeared as a circular, homogeneous, deeply basophilic body filling the cytoplasm and masking the nucleus within the epidermal poroma. These giant keratohyaline granules were observed either within the thickened granular layer of a pore near the surface (Fig. 3) or within the thickened granular layer in an area of premature keratinization (Fig. 8). Within the verruca vulgaris, however, these giant keratohyaline granules, which may also be combined with products of viral degeneration, tended to assume angular shapes.

Small, uniform basaloid epithelial cells, which tended to assume cuboidal or columnar shapes with generally well-defined cytoplasmic borders and intercellular bridges, formed a significant but quantitatively variable component within all epidermal poromas and many seborrheic keratoses. Melanized basaloid cells were observed within

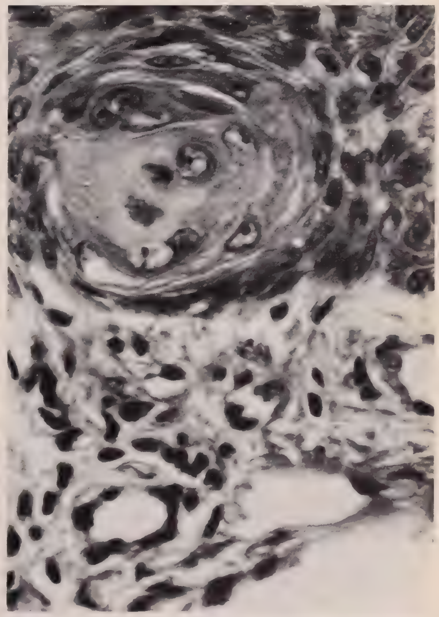

FIG. 5. Base of epidermal poroma detailing papillary dermal angioplasia and squamous eddy abutting basal layer and merging with adjacent basaloid cells. Note absence of basal cell destruction (H & E ×400).

some epidermal poromas and many seborrheic keratoses. The melanin appeared as fine, dust-like, golden-brown cytoplasmic particles tending to form a perinuclear cap. Glycogen, which in large amounts imparted a vacuolated appearance to the cytoplasm on H & E staining, could always be demonstrated within some of the epidermal keratinocytes (squamous or basaloid cells) of all lesions, and cytoplasmic vacuolization, with or without demonstrable glycogen, was observed within some of the basaloid and squamous cells of most epidermal poromas (Fig. 2) and some seborrheic keratoses. No glycogen could be demonstrated within the vacuolated granular layer cells of verrucae vulgares. A prominent palisaded basal layer above a thickened eosinophilic basement membrane zone (Figs. 2, 4) was seen on H & E sections within portions of many but not all epidermal poromas and clusters of mature sebaceous cells were observed at or near the base of many (Figs. 1B, 3, 6).

Dyskeratosis (abnormal keratinization) assumed different forms within the various lesions, including premature keratinization (large keratinized squamous cells within the malpighian layer), hyaline bodies (apoptotic cells), squamous eddy formation, and anaplastic (malignant) dyskeratotic changes. Premature keratinization was observed within all incipient stage keratocarcinomas, was never seen within the verrucae vulgares, and was variably present within the other lesions. It occurred without basal cell destruction in the incipient-stage keratocarcinomas and the epidermal poromas (Figs. 1, 2) and with basal cell destruction in irritated hypertrophic actinic and seborrheic keratoses, frequently associated with hyaline bodies within the malpighian layer and at the dermal-epidermal junction. Keratinocytic anaplasia without dyskeratosis and anaplastic dyskeratosis were encountered only in both types of keratosis. Whereas both changes were infrequent findings in the seborrheic keratoses, keratinocytic anaplasia without dyskeratosis was in-

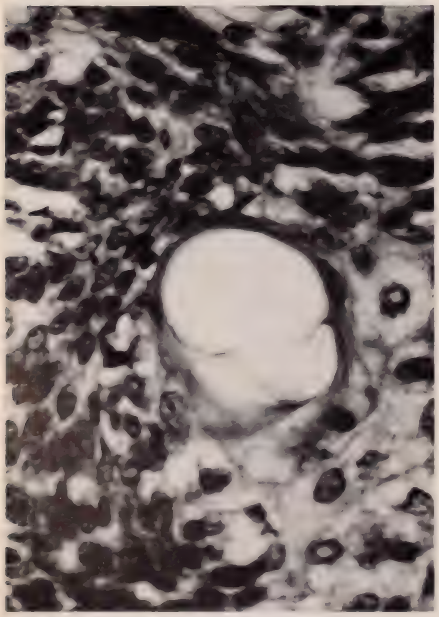
FIG. 6. Sebaceous cells and focally vacuolated basaloid cells abutting directly on hyaline lining of horn cyst containing scanty wisps of keratin near base of epidermal poroma (H & E ×400).

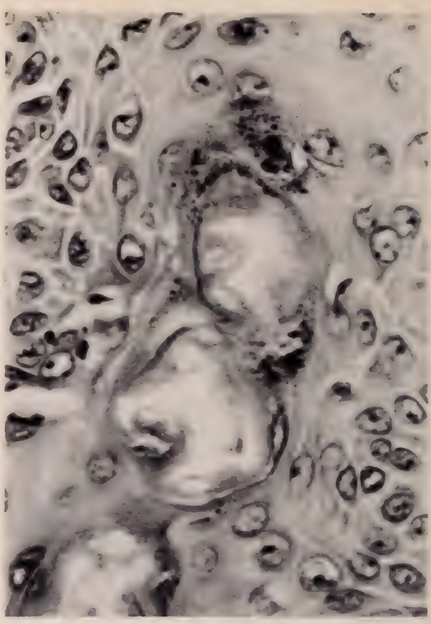
FIG. 7. Three cross sections through horn cyst containing abundant keratin lined by keratinized stratified squamous epithelium. Absence of granular layer in some areas and well-defined granular layer with large coarse keratohyaline granules in others. Partial hyaline lining in presence of poorly-defined granular layer at 6:00 o'clock within center section. This field is approximately midway between surface and base of epidermal poroma (H & E ×400).

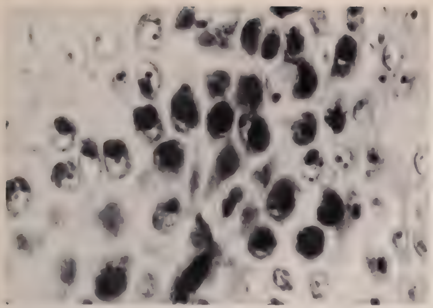

FIG. 8. Giant round keratohyaline granules occasionally obscuring nucleus within thickened granular layer in area of premature keratinization in epidermal poroma (H & E ×400).

variably present and anaplastic dyskeratosis was commonly observed within the hypertrophic actinic keratoses. Not seen in the other lesions, the latter frequently showed suprabasilar clefts with anaplastic acantholytic cells, many dyskeratotic.

Squamous eddies may be defined as small, circular, poorly defined clusters of keratinized squamous cells showing no atypism; they are confined to the epidermis and blend imperceptibly with adjacent basaloid cells or foci of premature keratinization. They were frequently conspicuous components of the epidermal poroma (Figs. 1B, 2), most often at the base and occasionally abutting the basal layer in the absence of basal cell destruction (Fig. 5), and also seen in the irritated seborrheic keratosis in the presence of basal cell destruction. Within the epidermal poroma they appear to represent, for the most part, attempts to form poral structures; many could be traced upward to small keratin-containing cysts (horn cysts) communicating with the skin surface (Fig. 3). At or near the surface, these cysts showed epidermal keratinization, frequently associated with hypergranulosis and giant round keratohyaline granules and occasionally with a hyaline lining. At or near the base, smaller horn cysts often communicated with the larger cysts above and frequently had a hyaline lining wholly or partly abutting mature sebaceous cells, basaloid cells (Fig. 6), and keratinized stratified squamous epithelium, with (Fig. 7) or without (Fig. 3) a granular layer. The hyaline lining tended to disappear with the advent of a well-defined granular layer. Horn cysts lined by keratinized stratified squamous epithelium without a hyaline lining and with or without a granular layer were also observed (Fig. 7). Within the seborrheic keratoses, squamous eddies were encountered primarily unassociated with horn cysts; these eddies seemed to represent a response to chronic irritation. In all lesions, squamous eddies rarely represented eccentric oblique sections through normal acrotrichia.

Keratin-containing cystic structures confined to the epidermis were present within some of all five lesions and were either true or false cysts. True cysts (horn cysts), those which produce or contain keratin, were encountered within epidermal poromas and seborrheic keratoses, primarily the acanthotic and reticulated types, and rarely within the other three lesions. Within the epidermal poroma, the keratin within the true cysts formed loose to compact concentric laminations admixed occasionally with parakeratotic cells and tended to be either absent or scanty within small cysts with a hyaline lining at or near the base and abundant, often filling the lumen, within the larger cysts at or near the surface.

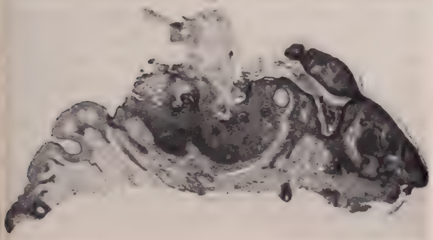

FIG. 9. Scanning view of mixed lesion showing characteristic features of epidermal poroma near the center of a seborrheic keratosis. Portion of seborrheic keratosis at right margin seems to dip lower than epidermal poroma (H & E ×20).

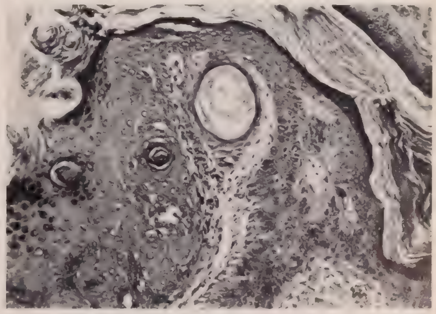

FIG. 10. Higher magnification of lesion in Fig. 9 detailing junction of epidermal poroma (left) with seborrheic keratosis (right) (H & E ×100).

Within the seborrheic keratoses, these cysts were largely formed by differentiating basaloid cells and occasionally represented cysts formed by occluded traversing acrosyringia and acrotrichia, also encountered rarely within the other lesions. The keratin within these cysts tended to be arranged in loose concentric laminations. False cysts (pseudocysts with keratin) were observed within some of all five lesions and represented either cross or oblique sections through verrucous or papillomatous proliferations or cross sections of normal traversing acrotrichia or acrosyringia. Except for those cysts described within the epidermal poroma, all keratin-containing cystic structures (true or false cysts) within the other lesions were lined by stratified squamous epithelium with a granular layer. A hyaline lining was noted only within some horn cysts of the epidermal poromas or rarely within horn cysts and pseudocysts with keratin of acrosyringial origin. With the PAS stain after digestion with diastase, the hyaline lining either did not stain or appeared weakly positive.

Papillary dermal angioplasia with focal ectasia was observed within all epidermal poromas and verrucae vulgares. Subepidermal capillary ectasia was always present within the incipient-stage keratocarcinomas and was variably present within the seborrheic and hypertrophic actinic keratoses. Rarely, mucin which had the staining characteristics of hyaluronic acid was prominent within the epidermal poromas and the seborrheic and hypertrophic actinic keratoses and was not observed within the other lesions. It was noted in the papillary tips or intercellularly within the epidermis, often forming pools in the epidermis. Not infrequently, individual lesions showed the characteristic histologic features of both an epidermal poroma and a seborrheic keratosis and were considered to be mixed lesions (Figs. 9, 10). Also observed and not uncommon were verrucae vulgares superimposed upon seborrheic keratoses.

Discussion

The pilosebaceous (with apocrine) and eccrine germ cells, although occurring separately, are first detectable within the basal layer of the fetal epidermis in the form of proliferating aggregates of small uniform basophilic cells which later differentiate into their respective adnexal structures. The remaining basal keratinocytes form the nonadnexal epidermis. I believe that each of these germ cells may form benign proliferations. Seborrheic keratoses represent purely intraepidermal proliferations of nonadnexal basal layer germ cells. Essentially, they are a form of epidermal nevus and, for all practical purposes, may be considered representative of all other forms of nonadnexal epidermal nevi. Hence, virtually all comments about seborrheic keratoses apply equally to epidermal nevi with the exception that, in my experience, varying degrees of hyperkeratosis and papillomatosis are always observed within epidermal nevi. Epidermal poromas represent intraepidermal proliferations of adnexal basal layer germ cells always associated with papillary dermal angioplasia, probably induced by the germ cells.

Contrary to what has been described in the literature, I was unable to identify adnexal proliferations which unequivocally differentiated toward specific poral structures. Hence, I have strong doubts about the existence of the hidroacanthoma simplex, the trichilemmoma, and the inverted follicular keratosis. Purely intraepidermal and relatively well-defined nests of basaloid cells (basaloid eddies), many of which contained large amounts of glycogen and which are considered to be a diagnostic criterion of the hidroacanthoma simplex, were frequent components of many seborrheic keratoses. Glycogenated clear basaloid cells and a prominent palisaded layer of basal cells above a conspicuously thickened basement membrane zone, supposedly diagnostic features of the trichilemmoma, were frequently observed in association with other histologic findings which are not characteristic of this entity: keratin cysts, some with a hyaline lining, premature keratinization, squamous eddies, and clusters of mature sebaceous cells. Also of interest: no glycogen or mucin could be demonstrated within many of the vacuolated basaloid cells, suggesting that intracellular edema, lipids, or both were present in significant amounts. Furthermore, the pilar sheath acanthoma, a lesion which unquestionably represents a trichilemmal proliferation, is not associated with papillary dermal angioplasia, which is always present within all epidermal poromas. Although most of these epidermal poromas dipped well below the level of the skin surface, the basement membrane zone was always intact and in no instance was I able to identify a pathogenetic relationship to the wall of a hair follicle, even in those cases with a large, central, keratin-filled cystic depression, both features considered to be the histologic hallmarks of the inverted follicular keratosis. In fact, many acanthotic and reticulated seborrheic keratoses often dipped well below the skin surface, as did the other four lesions.

When one carefully evaluates the histologic features of the epidermal poroma, it is clearly neither a wart nor a seborrheic keratosis. The basic histologic features essential for the diagnosis are acanthosis, most often a component of verrucous epidermal hyerplasia, in association with focal basaloid cell proliferation and papillary dermal angioplasia. Frequent but not constant features are epidermal dipping, cytoplasmic vacuolization of basaloid and squamous cells, a thickened basement membrane zone, premature keratinization, squamous eddies, horn cysts with a variable and often hyaline lining, hypergranulosis with giant round keratohyaline granules, and clusters of mature sebaceous cells at the base. Of the three possible poral structures which these pluripotential germ cells seemingly attempt to form, the sebaceous duct appears to be the target structure in most, if not all, cases, perhaps the acrosyringium in some cases, and (doubtfully) the acrotrichium in some cases. Although the epidermal poroma bears a histologic resemblance to a wart, the focal basaloid cell proliferation and the absence of inclusion bodies negate this diagnosis. The absence of papillary dermal angioplasia further distinguishes it from seborrheic keratosis. Additionally, when present individually or in any combination, giant round keratohyaline granules (not the angulated granules in warts), premature keratinization and squamous eddies in the absence of basal cell destruction, a thickened basement membrane zone, horn cysts with a hyaline lining (such as one observes within the normal acrosyringium and sebaceous duct) and clusters of sebaceous cells at the base would support the diagnosis of epidermal poroma and virtually exclude all of the other four lesions. In this regard, it is also of interest that the eccrine poroma, a well-known and histologically well-documented lesion with characteristic features, obviously not viral in etiology but pathogenetically related to the eccrine duct, often shows a combination of verrucous epidermal hyperplasia, premature keratinization, giant round keratohyaline granules, and papillary dermal angioplasia. Horn cysts (without a hyaline lining) were frequently encountered within seborrheic keratoses and epidermal poromas and rarely observed within the other three lesions.

Varying forms of dyskeratosis proved invaluable in the differential diagnosis of these lesions. Squamous eddies in the absence of basal cell destruction were common findings within the epidermal poromas and rare in the other lesions. In the poromas they largely represented poral differentiation of germ cell proliferations, in many instances traceable to horn cysts, with and without hyaline lining, often communicating with the skin surface in association with giant round keratohyaline granules. In all lesions, they rarely represented eccentric oblique sections through normal acrotrichia. Squamous eddies in the presence of severe basal-cell destruction were frequently observed within seborrheic keratoses and appeared to represent a response to chronic irritation. Premature keratinization in the absence of basal-cell destruction was observed only in all incipient-stage keratocarcinomas and many epidermal poromas. Premature keratinization and hyaline bodies were encountered only within the irritated seborrheic and hypertrophic actinic keratoses in association with severe basal-cell destruction. Keratinocytic anaplasia, with or without dyskeratosis, was always observed within the hypertrophic actinic keratoses, frequently with suprabasilar clefts containing anaplastic acantholytic cells, many of which were dyskeratotic. Keratinocytic anaplasia and anaplastic dyskeratosis were infrequent findings within the seborrheic keratoses. Anaplastic changes were not encountered within the other lesions.

Mixed lesions showing the histologic features of both an epidermal poroma and a seborrheic keratosis were relatively frequent. In my opinion, they represent a combination of adnexal and nonadnexal germ-cell proliferations occurring side by side. Although rarely encountered and not diagnostic, since it was also observed within the seborrheic keratoses and hypertrophic actinic keratoses, relatively large amounts of hyaluronic acid, often forming intraepidermal pools, could be demonstrated within the epidermal poromas. This most likely reflects the formation of increased amounts of stromal mucin with seepage through the epidermis akin to what one frequently encounters in digital mucous cysts. Since varying amounts of glycogen could always be demonstrated within some of the epidermal keratinocytes of all lesions, this observation was of no diagnostic value. Besides glycogen, intracellular edema or lipids or both probably account for the vacuolated appearance of many of the basaloid cells within the epidermal poroma.

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Submitted for publication March 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

The Anesthetic Management of Pulmonary Resection: Survey and Recommendations

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Abstract

The major medical centers of the United States were surveyed as to how they manage anesthesia for pulmonary resection. The results showed that most centers use a single-lumen endotracheal tube rather than a double-lumen endobronchial tube for airway management. For maintenance of anesthesia, most centers use inhaled volatile rather than intravenous anesthetic agents. These findings are discussed in relation to current knowledge of pulmonary physiology and surgical technique, and the use of double-lumen endobronchial intubation is recommended as the routine choice in the management of pulmonary resection.

We have conducted a simple survey of the anesthetic management of pulmonary resections as performed in the major medical centers of the United States. Questionnaires were addressed to members of the Society of Cardiovascular Anesthesiologists at each of 126 large medical centers in the United States; 102 replies were received, of which two were from centers at which no pulmonary resections were performed. In some centers, the questionnaire was completed by the addressee; in others it was passed on to a colleague who was involved with this area of anesthesia. The questions were brief and requested (a) number of pulmonary resections per annum, (b) percentage use of double-lumen endobronchial and single-lumen endotracheal intubation, and (c) percentage use of volatile agents. The results described are based on the 100 centers at which pulmonary resection was undertaken.

Table I shows the use of the double-lumen tube (DLT) in relation to case load. Only 39 of the centers use DLT in more than 50% of their cases, and 33 centers handle pulmonary resections with endotracheal rather than endobronchial intubation. Furthermore, the data offer insufficient evidence to state that the percentage use of the DLT is associated with number of pulmonary resections performed (χ^2 (6 df) = 9.35; $p < 0.10$).

Our findings for the United States differ considerably from those of a similar survey conducted by Pappin in the United Kingdom (1). Pappin found that in cases of pulmonary resection, endobronchial intubation was the most frequently used technique. The Robertshaw DLT was the most popular of the double-lumen tubes in current use in the United Kingdom. Furthermore, 53.5% of anesthetists in his survey agreed that their choice of tube was influenced by surgical preference and junior staff training commitments. All indicated that patient welfare and safety were the most important considerations regardless of other factors.

The reluctance to accept the routine use of the DLT and one-lung anesthesia (OLA) in the United States may be based upon concern about hypoxemia, increased resistance to gas flow through smaller cannulae, and technical difficulties in passing and positioning these tubes. If lack of experience with these tubes were the major factor, one might expect that those centers performing

TABLE I
Use of Double-Lumen Tube by Caseload

Use of DLT (%)	No. of Pulmonary Resections Per Annum <20	21–50	51–100	>100	Totals
<30%	5	13	11	12	41
30–70%	0	11	11	4	26
>70%	5	9	8	11	33
Totals	10	33	30	27	100

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TABLE II
Median and Mean % Use of Volatile Agent

	Percentage Use of Double-Lumen Tube						
	Never (n = 5)	1%–10% (n = 25)	11%–30% (n = 18)	31%–69% (n = 16)	71%–90% (n = 16)	91%–99% (n = 8)	Always (n = 12)
Median	60%	70%	83%	85%	88%	93%	100%
Mean	69%	64%	71%	77%	81%	80%	79%

the most pulmonary surgery would provide the greatest experience with and show the largest incidence of use of the DLT. This assumption, however, was not borne out by our results.

Concern about hypoxemia during OLA may deter anesthesiologists from using the DLT. Several studies have shown an incidence of unacceptably low PaO_2 in 15%–25% of cases during OLA(2, 3). We believe that this high incidence of hypoxemia is associated with the use of volatile inhalational agents for anesthesia maintenance, since volatile anesthetic agents have been widely shown to obtund the hypoxic pulmonary vasoconstrictor reflex (4). Several recent studies have suggested that intravenous anesthetic agents do not depress hypoxic pulmonary vasoconstriction, and indeed that ketamine may even potentiate this response (5, 6).

The results of our survey regarding maintenance technique show that the mean percentage use of volatile agents is 74%, and the mean for intravenous agents is 26% (Table II). The use of volatile agents is highly correlated with the use of the OLA technique ($r = 0.81$). The median and mean percentage use of volatile agents is tabulated against case load in Table II; the median has been calculated because of the skewness of the data.

We believe that all patients undergoing thoracotomy for pulmonary resection in the lateral position should be managed using a double-lumen endobronchial tube. This permits control of each lung independently and offers medical, surgical, and physiologic advantages. Its use is mandatory for patients with excessive secretions, as for example in cases of bronchiectasis, bronchopleural fistula with empyema, air- or fluid-containing poleachynal cysts or intrapulmonary bleeding. In these latter situations, the use of a double-lumen tube prevents contamination of the down-lung.

The use of the DLT, however, need not imply *one-lung* ventilation only, but *split-lung* ventilation as originally conceived by Carlens. A reduction in size of the lung being operated on, achieved by using the DLT, permits easier use of the surgical stapler and facilitates access to the hilar region. Reduction in lung size is also useful in nonpulmonary thoracic surgery. Thus, split-lung ventilation makes the approach to the esophagus during a thoraco-abdominal esophageal procedure much easier for the surgeon.

As with any specialized technique, practice makes perfect, and in our experience there have been very few technical problems in managing these tubes. It should be noted, however, that the use of these tubes and OLA is not applicable to children or to very small adults.

The incidence of hypoxemia during OLA can be minimized by the use of intravenous rather than inhaled volatile anesthetic agents. Of the 100 questionnaires returned, 92 indicated routine monitoring of arterial blood gases. If hypoxemia is detected during OLA, an F_IO_2 of 1.0 can be used in combination with intravenous ketamine in the confident knowledge that the patient will be asleep and analgetic. If the hypoxemia persists, two-lung ventilation can always be resumed.

The use of double-lumen endobronchial intubation should be routine in the management of pulmonary resection in adult patients.

Acknowledgments

We are indebted to Dr. Harry Smith, Jr., for his statistical assistance.

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Submitted for publication April 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Renal Salt Wasting and Metabolic Acidosis with Trimethoprim-Sulfamethoxazole Therapy

ALLEN M. KAUFMAN, M.D., GERARD HELLMAN, M.D., AND RUTH G. ABRAMSON, M.D.

After extensive use in England and Europe, Cotrimoxazole, a combination of trimethoprim and sulfamethoxazole, was introduced into the United States ten years ago (1) and marketed under the new brand names Septra and Bactrim. The standard tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole. The usual adult dose is 2 tablets every 12 hours, but this should be reduced in patients with diminished renal function. Higher doses have been used under certain circumstances and double strength (DS) tablets are manufactured.

The first reports of nephrotoxicity appeared in 1969 (2), when Hanley described one patient with crystalluria and four with oliguria. In 1973 Kalowski et al (3) described sixteen patients with nonoliguric deterioration of renal function. Two of these patients had renal biopsies performed; both biopsies yielded a histologic finding of acute tubular necrosis. Since then reports of various nephrotoxic effects of trimethoprim-sulfamethoxazole, including interstitial nephritis (4), have been published. We present here the first case report of renal salt wasting and metabolic acidosis, unassociated with the production of organic renal disease, apparently caused by trimethoprim-sulfamethoxazole.

Case Report

Six months prior to the current admission this 69-year-old woman developed lymphocytic leukemia with lymphadenopathy and hepatosplenomegaly. At that time, urine analysis, blood urea nitrogen (BUN), and intravenous pyelogram were normal. Chlorambucil and prednisone effected a good clinical response.

Four months prior to the current admission the patient was admitted to the hospital with leukopenia and a reticulonodular pulmonary infiltrate. A transbronchial lung biopsy was nondiagnostic for leukemia, viral inclusions, and pneumocystis. Chlorambucil was discontinued and prednisone maintained at 15 mg per day. Empirical treatment with antibiotics and white-cell transfusions did not result in any clinical improvement and on the eighth hospital day Septra DS, 2 tablets every 6 hours, was added to the regimen. At that time the BUN was 7 mg per deciliter, serum creatinine 0.9 mg per deciliter, serum sodium 135 mmol, potassium 3.1 mmol, chloride 94 mmol, and carbon dioxide content 36 mmol per liter. Plasma pH was 7.55. Two days later the fever resolved and all medications were discontinued except for Septra and prednisone. Nine days after Septra had been instituted the patient was noted to be oliguric and clinically volume-depleted with orthostatic blood pressure changes and an 8-kg weight loss. The BUN was 25 mg per deciliter, serum creatinine 1.6 mg per deciliter, serum sodium 122 mmol, potassium 6.5 mmol, chloride 90 mmol, and carbon dioxide content 19 mmol per liter. Plasma pH was 7.36. There were no cells or crystals in the urine sediment. Septra was discontinued, prednisone was increased to 30 mg per day, and urine output increased promptly concomittant with the administration of saline intravenously. Within 3 days the patient had gained 2.3 kg. The BUN was 15 mg per deciliter, serum creatinine 0.7 mg per deciliter, serum sodium 137 mmol, potassium 4.0 mmol, chloride 108 mmol, and carbon dioxide content 24 mmol per liter. At discharge, the pulmonary infiltrate had cleared and the prednisone was tapered and discontinued.

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Three weeks prior to the current admission the patient again developed a reticulonodular pulmonary infiltrate. She was treated with Bactrim, 4 tablets every 8 hours, and noted progressive weakness and orthostatic dizziness. On admission, the physical exam was notable for signs of volume depletion, including postural hypotension. Her weight was 46.8 kg, having decreased from 49.5 kg, and she was oliguric. The BUN was 35 mg per deciliter, creatinine 3.1 mg per deciliter, serum sodium 132 mmol, potassium 7.0 mmol, chloride 101 mmol, and carbon dioxide content 18 mmol per liter. Plasma pH was 7.33. The urine sediment had many urate crystals, although the serum uric acid was normal (6.2 mg per deciliter). The urine had 1–2 white blood cells per high powered field, a specific gravity of 1.021, and a pH of 6.0. Urine sodium, potassium, and chloride concentrations were 137 mmol, 40 mmol, and 49 mmol per liter, respectively. Bactrim was discontinued and the patient was treated with intravenous fluids and steroids. With volume repletion there was a prompt increase in urine output. Three days after admission she had gained 3.6 kg; the BUN was 19 mg per deciliter, serum creatinine 1.0 mg per deciliter, serum sodium 144 mmol, potassium 3.8 mmol, chloride 106 mmol, and carbon dioxide content 28 mmol per liter. There were no crystals in the urine. Plasma cortisol and aldosterone drawn on admission were 22.5 ng per deciliter (normal = 6–16 ng per deciliter) and 43.9 ng per deciliter (normal = 4–31 ng per deciliter), respectively. A subsequent ACTH stimulation test was normal.

The patient has been followed as an outpatient and remains without electrolyte abnormalities or evidence of renal disease.

Comment

On two separate occasions this patient developed a respiratory illness and was treated with a high dose of trimethoprim-sulfamethoxazole, each time associated with rapid weight loss without extrarenal fluid losses. When urine electrolytes were measured, the urine sodium concentration was high despite oliguria and concentrated urine. Intravenous fluid administration rapidly corrected the elevated BUN and creatinine, thereby suggesting that the azotemia was not consequent to organic disease of the kidney. Rather, the azotemia appears to have resulted from volume depletion secondary to renal sodium and water loss. In view of the normal adrenal function, volume depletion appears to have been produced by a diuretic action of trimethoprim-sulfamethoxazole. Although it has been suggested that trimethoprim-sulfamethoxazole can cause a modest natriuresis (5), no case of profound diuresis has heretofore been described.

Of further interest was the development of metabolic acidosis with hyperkalemia. The development of hyperkalemia in association with metabolic acidosis and hyponatremia suggested the diagnosis of adrenal insufficiency, but the normal plasma cortisol and aldosterone excluded this possibility. Although carbonic anhydrase inhibition by sulfamethoxazole (6) may have contributed to the development of acidosis, carbonic anhydrase inhibitors generally cause hypokalemia. It is conceivable that trimethoprim-sulfamethoxazole affects potassium secretion either directly or via antagonizing the effects of aldosterone on the distal nephron. Alternatively, hyperkalemia may have developed during the period of oliguria, when potassium excretion might have been impaired.

This case suggests that trimethoprim-sulfamethoxazole may result in significant fluid and electrolyte abnormalities. Patients receiving high doses of trimethoprim-sulfamethoxazole may be at particular risk and should be evaluated for these potential complications during a course of treatment.

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Submitted for publication September 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Changes in Serum Bile Acids During Treatment with Chenodiol or Ursodiol for Dissolution of Cholesterol Gallstones

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Abstract

Chemical dissolution of gallstones by feeding of chenodiol or ursodiol can be monitored by measuring the composition of bile acids in bile or serum. Changes in the composition of bile acids in bile already have been reported. We have measured the composition of bile acids in serum. Nineteen serum samples from 11 patients, 7 treated with chenodiol and 4 with ursodiol, were analyzed. The analyses included column liquid chromatography, solvent extraction, thin-layer chromatography, and gas liquid chromatography. The mean recovery of hyodeoxycholic acid standard was 73%. Treatment with chenodiol doubled the concentration of this bile acid ($p < .02$) and significantly increased ursodeoxycholic acid ($p < .50$). Treatment with ursodiol increased this bile acid several fold ($p < .50$). Both chenodiol and ursodiol treatment increased the total concentration of bile acids in serum. Studies of biliary bile acids showed that chenodiol treatment doubles its percentage composition and increases ursodiol, and ursodiol treatment increases ursodiol to up to 50% of total bile acid composition. Changes in the serum concentration of chenodiol and ursodiol can be used as indices of compliance.

Serum bile acids can be measured by chromatographic methods and radioimmunoassays. The former are cumbersome because of high protein concentrations, whereas the latter are limited to measurement of cholic acid only. Fluorimetric methods are imprecise and incapable of quantifying the individual bile acids (1–7).

During chemical dissolution of gallstones by feeding of chenodeoxycholic (chenodiol) or ursodeoxycholic acid (ursodiol), compliance and efficacy can be monitored by measuring the composition of bile acids in bile or serum. In bile, chenodiol rises to more than 70% of total bile acids when this bile acid is fed. With ursodiol feeding, this bile acid makes up more than 40% of total bile acids whereas the sum of ursodiol and chenodiol rises to more than 70% (8–15).

Changes in composition of serum bile acids resulting from feeding of bile acids are not well defined. Because of different hepatic clearance of the two primary bile acids, changes in the composition of biliary bile acids during feeding of either chenodiol or ursodiol are not identical to those in serum (16–21).

Methods

Eleven patients were studied; 7 received chenodiol, 15 mg/kg/day, and 4 were treated with ursodiol, 10 mg/kg/day. The duration of treatment varied from 1 to 11 months. Nineteen blood samples were drawn after 8 hours overnight fasting, before and during treatment; the samples drawn before treatment were used as the control group. The serum was stored at 0–4° C for as long as 2 months prior to assay by column liquid chromatography, thin-layer chromatography, solvent extraction, and gas-liquid chromatography.

Column Liquid Chromatography. Amberlite XAD-7, a nonionic resin, was soaked in water to remove NaCl and $NaHCO_3$(4). The impurities were removed by repeated swirling and decanting of the supernatant so that the beads sedimented within 20–30 sec. The resin was then treated with methanol, chloroform:methanol (1:1 v/v), meth-

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anol, and finally water. The resin was kept under water until used.

For column extraction, liquid chromatography columns were set up. The resin was poured in up to a height of 15 cm and kept under water until the serum was prepared. Aliquots of 5 ml serum were taken from each sample. Twenty-five μl of hyodeoxycholic acid was added to serve as an internal standard. Subsequently, the serum was diluted 1:10 with 0.1N NaOH in saline, and allowed to stand for 30 min. The dilute serum was poured onto the column, and the flow rate was adjusted to 0.1ml/min (3–4 drops/min). When the serum was eluted, the resin was washed with 5 ml of 0.1 N NaOH. The bile acids were extracted with 100 ml of methanol and collected in a 250-ml round-bottom flask. The methanol was evaporated down to a volume of 5 ml. The remaining methanol was transferred to a teflon tube and evaporated to dryness under air at 40° C. The sediment was dissolved in 2 ml of 2N NaOH and subjected to vigorous hydrolysis at 259° F and pressure of 15 lb/in^2 for 3 hours.

Solvent Extraction. After hydrolysis, the solution was transferred from teflon to glass tubes. Extraction with 5 ml of hexane was done twice to remove nonpolar steroids. Acidification with about 20 drops of concentrated HCL to pH 2 was carried out. Bile acids were extracted with 5 ml of ethyl acetate (twice). The solvent was evaporated under air at 40° C. The bile acids were then methylated. The dry organic layer was dissolved in 1 ml methanol, to which 0.7 ml of 2, 2-dimethoxypropane was added, followed by 1 drop of 1:1 HCl:methanol v/v solution. The test tubes were covered immediately to prevent exposure to the moist air. They were allowed to stand for 30 minutes, and evaporated under air at 40° C.

Thin-Layer Chromatography. Separation of bile acids by thin-layer chromatography was carried out in hexane:ethyl acetate (9:1 v/v). The methylated bile acids were dissolved in 4 drops of Folch (methanol:chloroform, 1:1 v/v), and transferred to a silica gel plate 0.250 mm thick, 20 × 20 cm. The plates were air dried and exposed to iodine vapor. Using bile acid standards, the individual bile acids were eluted from the plates with methanol (5 ml, twice).

Gas Liquid Chromatography. The methanol eluates were evaporated to dryness and the bile acids were transferred to gas liquid chromatography vials using Folch solution. Twenty-five μl of 5α-cholestane was added and the solution was evaporated. The bile acids were trimethyl-sillylated, evaporated, and dissolved in 100 μl of ethyl acetate. This was followed by quantitation of bile acids as their trimethyl-sillyl derivatives using 5α-cholestane as an internal standard on a glass column at 273° C (nitrogen as carrier gas).

Recovery. The mean recovery of hyodeoxycholic acid was 73%, based on 17 samples. The other 2 samples had unacceptable recovery and were excluded from the calculations.

Results

Treatment with chenodiol doubled the concentration of this bile acid, compared to the pretreatment control level ($p < .02$). Ursodeoxycholic acid increased significantly during treatment with chenodiol ($p < .5$). Changes in cholic acid concentrations were not significant; lithocholic acid was measurable in only one patient during treatment. Changes in percentage composition paralleled changes in absolute concentrations (see Tables I and III).

Treatment with ursodeoxycholic acid (Table II) resulted in a several-fold increase of this bile acid, compared to the pretreatment control level ($p < 0.50$) as shown in Table III. The concentration of chenodiol remained unaltered. An unexpected rise in the levels of cholic acid was observed. Deoxycholic acid was measurable in two out of four patients, and lithocholic acid was present in one patient. The changes in the percentage composition paralleled the changes in absolute concentration with respect to both ursodiol and cholic acid. Chenodiol showed a decrease in the percentage composition.

Both chenodiol and ursodiol administration led to an increase of the total concentration of the bile acids in serum.

Discussion

Normal human bile contains chenodiol, cholic, and deoxycholic acid in a ratio of about 40:40:20. Lithocholic acid and ursodiol make up a small fraction of total bile acids (9, 11–14, 20, 22).

Changes in the composition of biliary bile acids have been observed upon bile acid feeding. When chenodiol is administered, its percentage composition doubles, and the percentages of cholic and deoxycholic acid decline to one third of their pretreatment values. An increase in the composition of lithocholic acid and ursodiol is shown in Table IV (9, 11, 12, 20, 22). When ursodiol is administered, this bile acid increases markedly up to about 50%. Chenodiol, cholic, and deoxycholic acids decrease by one half of their original levels. No sig-

TABLE I

*Effect of Chenodiol on Concentration and Percentage Composition of Bile Acids in Serum**

Patient No.	Unit	Chenodiol Control Concentration (%)	Chenodiol Treatment Concentration (%)	Cholic Control Concentration (%)	Cholic Treatment Concentration (%)	Ursodiol Control Concentration (%)	Ursodiol Treatment Concentration (%)
1	μg/ml	2.08 (28)	3.41 (45)	5.31 (72)	4.22 (55)	—	—
	μmol/l	5.32 (29)	8.72 (46)	13.0 (71)	10.3 (54)	—	—
2	μg/ml	1.13 (14)	3.65 (37)	6.46 (80)	6.23 (63)	0.49 (6)	—
	μmol/l	2.77 (14)	9.34 (38)	15.8 (80)	15.3 (62)	1.25 (6)	—
3	μg/ml	2.93 (56)	3.39 (48)	2.33 (44)	3.67 (52)	—	—
	μmol/l	7.49 (57)	8.67 (49)	5.71 (43)	9.00 (51)	—	—
4	μg/ml	1.28 (16)	3.42 (35)	6.15 (79)	6.15 (63)	0.36 (5)	0.27 (3)
	μmol/l	3.27 (17)	8.75 (36)	15.1 (78)	15.1 (62)	0.92 (5)	0.69 (3)
	μg/ml	—	3.88 (36)	—	5.00 (46)	—	0.75 (7)
	μmol/l	—	9.92 (36)	—	12.3 (45)	—	1.92 (7)
5	μg/ml	0.85 (14)	—	4.49 (74)	—	0.68 (11)	—
	μmol/l	2.17 (15)	—	11.0 (74)	—	1.74 (12)	—
6	μg/ml	—	3.39 (36)	—	5.99 (64)	—	—
	μmol/l	—	8.67 (37)	—	14.7 (63)	—	—
7	μg/ml	—	8.12 (37)	—	9.88 (46)	—	3.70 (17)
	μmol/l	—	20.8 (38)	—	24.2 (44)	—	9.46 (17)
Mean ± SD		1.65 ± 0.76 (23)	4.18 ± 1.63 (36)	4.95 ± 1.48 (70)	5.88 ± 1.88 (51)	0.51 ± 0.13 (7)	1.57 ± 1.52 (13)
		4.20 ± 1.95 (24)	10.7 ± 4.15 (37)	12.1 ± 3.62 (69)	14.4 ± 4.60 (49)	1.30 ± 0.34 (7)	4.02 ± 3.88 (14)
P value		<0.02		NS		<0.05	

* Deoxycholic acid not detectable; lithocholic acid detected in only one patient (1.18 μg/ml during treatment).

TABLE II

Effect of Ursodiol on Concentration and Percentage Composition of Bile Acids in Serum

Patient No.	Unit	Chenodiol Control Concentration (%)	Chenodiol Treatment Concentration (%)	Cholic Control Concentration (%)	Cholic Treatment Concentration (%)	Ursodiol Control Concentration (%)	Ursodiol Treatment Concentration (%)
1	μg/ml	1.45 (40)	1.91 (17)	2.20 (60)	7.75 (69)	—	1.56 (14)
	μmol/l	3.55 (40)	4.88 (17)	5.39 (60)	19.0 (68)	—	3.99 (14)
2	μg/ml	1.21 (24)	1.03 (3)	3.83 (76)	31.8 (86)	0.03 (1)	3.41 (9)
	μmol/l	3.09 (25)	2.63 (3)	9.39 (75)	77.9 (86)	0.08 (1)	8.72 (10)
3	μg/ml	3.52 (48)	3.23 (27)	3.82 (52)	7.81 (65)	—	0.57 (5)
	μmol/l	9.00 (49)	8.26 (28)	9.36 (51)	19.1 (64)	—	1.46 (5)
4	μg/ml	—	1.66 (7)	—	18.8 (83)	—	1.88 (8)
	μmol/l	—	4.25 (7)	—	46.0 (82)	—	4.81 (9)
Mean ± SD		2.06 ± 1.03	1.96 ± 0.80 (10)	3.28 ± 0.77 (61)	16.5 ± 9.89 (81)	0.03 (1)	1.86 ± 1.02 (9)
		5.21 ± 2.69 (39)	5.01 ± 2.05 (10)	8.05 ± 1.88 (61)	40.5 ± 24.2 (81)	0.81 (1)	4.75 ± 2.61 (9)
P Value		<0.05		NS		<0.05	

TABLE III

Comparison of Pretreatment and Treatment Concentrations and Percentage Composition of Three Bile Acids in Serum

	Unit	(Mean ± SD) Chenodiol Concentration (%)	(Mean ± SD) Cholic Concentration (%)	(Mean ± SD) Ursodiol Concentration (%)	Total
Pretreatment					
Control	μg/ml	1.81 ± 0.87 (28)	4.32 ± 1.26 (66)	0.39 (6)	6.52
(8 analyses)	μmol/l	4.58 ± 2.26 (28)	10.6 ± 3.08 (66)	1.00 (6)	16.2
Chenodiol	μg/ml	4.18 ± 1.63 (36)	5.88 ± 1.88 (51)	1.57 ± 1.52 (13)	11.6
(7 analyses)	μmol/l	10.7 ± 4.15 (37)	14.4 ± 4.60 (49)	4.02 ± 3.88 (14)	29.1
Ursodiol	μg/ml	1.96 ± 0.80 (10)	16.5 ± 9.89 (81)	1.86 ± 1.02 (9)	20.3
(4 analyses)	μmol/l	5.01 ± 2.05 (10)	40.5 ± 24.2 (81)	4.75 ± 2.61 (9)	50.3

TABLE IV

Reported Effects of Chenodiol on Percentage of Five Bile Acids in Bile

		Chenodiol		Cholic		Deoxycholic		Lithocholic		Ursodiol	
Reference	Author & Year	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %
(9)	Stiehl et al 1978	41	84	37	5	20	2	1	2	1	5
(20)	Mok et al 1979	37	63	35	21	24	12	2	3	2	2
(11)	Carulli et al 1980	35	73	40	11	23	8	2	8	—	—
(12)	Stiehl et al 1980	43	87	—	—	—	—	—	—	1	2
(22)	Ahlberg et al 1981	35	82	35	6	28	7	—	3	—	2
	Mean	38	78	37	12	24	7	2	4	1	3

nificant changes in lithocholic acid composition are noted, as shown in Table V (9, 11–14).

Changes in the composition of serum bile acids have been observed upon bile acid feeding. When chenodiol is administered, its concentration increases threefold. When ursodiol is fed, its levels increase to about 50% of total bile acids; chenodiol and cholic acid decrease by one half; and deoxycholic acid decreases by one fourth. Lithocholic acid becomes measurable and contributes as much as 2% (1, 2, 13, 15, 24, 25).

In our study, the analysis was limited to serum bile acids. In the pretreatment samples, cholic acid was the predominant bile acid; the concentration of chenodiol was about half that of cholic acid, and the remaining fraction was ursodiol. Deoxycholic acid was not measurable. Our results for serum bile acids differ from those reported by others (1, 2, 13, 15, 24, 25). The difference may be methodological; however, our results are more compatible with the preferential crossing of trihydroxy over dihydroxy bile acids across the sinusoidal membrane.

We observed changes in the composition of serum upon bile acid feeding. When chenodiol was administered, its concentration doubled and its percent composition increased. There was some increase in the amount of cholic acid, but its percentage decreased. Ursodiol concentration increased four-fold and its percentage composition also increased. These changes correspond to those observed in other studies.

When ursodiol was administered, there was a significant increase in its concentration and percentage composition. The concentration of chenodiol acid remained the same and its percentage composition decreased. These changes paralled those observed by others. However, there was an unexpected increase in the concentration and percentage composition of cholic and deoxycholic acids; other authors report a corresponding decrease.

Feeding of either chenodiol or ursodiol resulted in a significant increase of the concentration of total bile acids in serum. All the changes we observed can be used for monitoring the effectiveness of bile acid treatment in the dissolution of cholesterol stones.

Measures of compliance and efficacy have to date been based on changes in the concentration

TABLE V

Reported Effects of Ursodiol on Percentage of Five Bile Acids in Bile

		Chenodiol		Cholic		Deoxycholic		Lithocholic		Ursodiol	
Reference	Author & Year	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %	Control %	Treatment %
(9)	Stiehl et al 1978	41	18	37	16	20	8	1	1	1	57
(13)	Makino et al 1978	54	44	26	14	19	12	1	1	—	29
(12)	Stiehl et al 1980	43	16	—	—	—	—	—	—	1	64
(14)	Bateson et al 1980	43	31	29	20	22	17	2	3	2	30
		43	19	35	15	19	13	2	3	2	50
(11)	Carulli et al 1980	35	22	40	14	23	8	2	2	—	54
	Mean	43	25	33	15	22	13	2	2	2	46

of biliary chenodiol and ursodiol, as shown in Tables IV and V. Changes in the serum concentrations of chenodiol or of ursodiol can be used as indices of compliance. The prediction of efficacy for gallstone dissolution could not be established in this limited study because of the small number of patients and the short duration of treatment.

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Submitted for publication October 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Catheter and Cradle: Nonsurgical Retrieval of Foreign Bodies

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Abstract

Several cases of nonsurgical retrieval of foreign bodies from the heart, blood vessels, gastrointestinal tract, and tracheobronchial tree have been reported. Loops snare technique, grasping forceps, and Dormia basket have all been used for this purpose. This is a report of nonsurgical retrieval of a broken CVP line from the heart to reemphasize the simplicity of the technique, to describe the procedure, and to suggest the use of a cradle table to help expedite the procedure when biplane fluoroscopy is not available. With the increasing use of intravascular monitoring catheters in the acutely ill patient, the problem of lost foreign bodies in the vascular system will occur with increasing frequency.

Case Report. A 74-year-old white woman was in our Surgical Intensive Care Unit with terminal carcinoma of the esophagus and chronic obstructive pulmonary disease. An internal jugular line was in place on the right. The catheter had broken off and chest x-ray showed a 16 cm piece of radiopaque tubing in the superior vena cava. A cutdown was performed in an unsuccessful attempt to retrieve the lost tubing. A postcutdown control chest x-ray (Fig. 1) confirmed the rapid migration of the piece of catheter to the right side of the heart with the tail in the superior vena cava. The condition of the patient precluded any major surgical intervention. The patient was taken to the cardiac catheterization laboratory. Under fluoroscopic control, a Curry catheter and snare wire was passed into the right atrium via percutaneous vena puncture of the right femoral vein. The broken CVP line was snared and removed in less than 20 minutes without complication. During the passage of the catheter through the right side of the heart, there were occasional induced atrial premature beats which did not require any management.

The cradle table of the fluoroscopic unit helped to localize the position of the retrieval catheter with respect to the broken line by viewing in multiple projections. The patient was originally examined in anteroposterior position. After several missed attempts at snaring the catheter, the cradle was rotated into the 45° left anterior oblique projection, which showed the snare posterior to the catheter. The snare was then easily repositioned anteriorly with immediate retrieval of the broken catheter.

Technique. A straight catheter was advanced into the IVC to the level of the right atrium via the femoral venous route. A 240 cm guide wire with a loop snare (Fig. 2) was passed through the catheter. By advancing or retracting either limb of the wire, one can increase or decrease the diameter of the loop. The larger the loop, the easier it is to snare the foreign body. If single plane fluoroscope is used, a compound, convoluted loop can be used more efficiently. After snaring the piece of tubing, the snare loop was brought down to the genu of the tube. Both limbs were pulled down until the snare was closed. The whole device was removed from the vascular system in one quick motion. The procedure lasted less than 20 minutes. As previously mentioned, the cradle tube permitted us to visualize the relationship of the two objects in different planes and helped expedite the procedure. A similar advantage could be obtained with the use of an X-arm fluoroscope. Bleeding at the catheter site was minimal.

Summary. With the widespread use of indwelling venous catheters, the possibility of cath-

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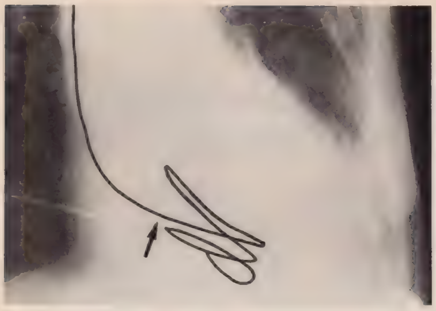

FIG. 1. Tubing (arrow) lodged in right side of the heart with a tail in the superior vena cava.

eter breakage or embolus, although uncommon, remains a possibility. Nonsurgical retrieval, with the aid of a cradle or C-arm, may result in prompt removal and avoid the necessity of surgical intervention. Catheter embolus is a serious complication. Catheter emboli can lodge in a large vein, the heart, or a pulmonary artery. This may be the cause of fatal cardiac arrhythmias or act as foci for thrombosis embolus, infection, or perforation.

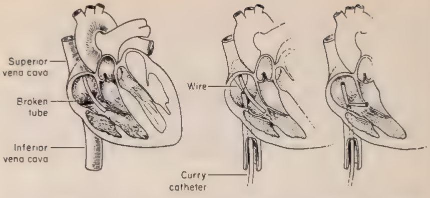

FIG 2. Position of tube in cardiovascular system; **left**, guide wire with loop snare overriding tubing; **middle**, tubing caught in closed snare by pulling wire limbs; **right**, whole device removed in a quick withdrawal motion.

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Submitted for publication April 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Leiomyosarcoma of the Duodenum: Two Cases, One with Echographic Image

MOSHE ROSENBLATT, M.D., HERMAN ROTHFELD, M.D., FRIDEL KRETZER, M.D., MIRIAM LURIE, M.D., AND J R. KAFTORI, M.D.

Abstract

Leiomyosarcoma of the duodenum is a very rare tumor. A little more than one hundred cases have been reported in the world literature. Two cases are reported, one of them with echographic image. The principal patterns and the management of this kind of tumor are presented here with a review of the literature.

The first case of leiomyosarcoma of the duodenum was reported in 1920 by Ernest von Salis (1). Up to 1971 there were approximately 95 cases reported in the literature (2). Considering the cases reported since then, particularly in lesser known medical journals (3–8), we assume that a little more than one hundred cases have been reported to date. To our knowledge, none of them has included an echographic study. There are no general or specific symptoms or criteria for the clinical diagnosis of intestinal myomatous tumors and the majority of the reported cases were not diagnosed even during operation. Treatment has varied from local to wide resection, depending on the individual case.

Case 1. A 44-year-old white man, born in Rumania, with no previous history of illness except for hypertension, consulted his physician because of nausea and vomiting which had begun five months earlier. There were no pain, fever, diarrhea, constipation, jaundice, or weight loss. His physician palpated a large abdominal tumor. Routine laboratory examination (blood, urine, and feces) was normal. A gastrointestinal series showed no filling defects or deformities. Ultrasonography showed a large, well-delineated mass, 6 × 7 × 7 cm caudal to the right liver lobe and anterior to the right kidney. The mass was mainly sonolucent but showed multiple echoes within it. Some of these echoes were linear, denoting septa. The liver, gallbladder, and right kidney were normal (Fig. 1). A Weinberg test was negative but a Casoni test was positive and the patient was admitted to the hospital with the preliminary diagnosis of echinococcal cyst of the liver. On physical examination, the only abnormal finding was a big soft tumor occupying the whole of the right upper quadrant, separated from the liver.

On the subsequent day the patient underwent surgery. Through a right subcostal incision, a large retroperitoneal tumor was found, the size of a baby's head (Fig. 2). The anterior surface of the tumor was partially attached to the transverse colon and the posterior surface to the vena cava and duodenum. In order to excise the whole tumor, a patch of the anterior duodenal wall, to which the tumor was attached, had to be removed. The papilla of Vater was visible through the duodenal hole and seemed to be normal. The duodenal defect was then repaired. See Figs. 3, 4.

The postoperative period was complicated by septic fever. X-ray examination revealed an abscesslike cavity in the right lower quadrant and a Gastrografin meal showed a strange filling defect in the ascending colon, followed by normal large bowel transit. The patient was reoperated on and the cecum was found to be totally disrupted from the ascending colon (probably as a result of accidental binding of the right colic artery in the first operation). A right hemicolectomy was performed. However, the patient deteriorated, with fever and nonobstructive jaundice, and had to be operated upon for the third time.

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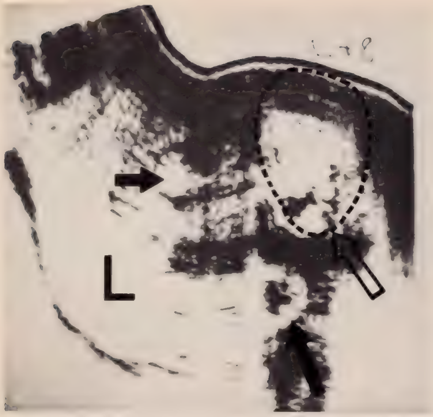

FIG. 1. Longitudinal scan 8 cm right to the midline, showing mass (white arrow) anterior to the right kidney (large black arrow) and caudal to the liver (L). The mass is mainly transsonic. Linear echoes within mass show septa formation. The gallbladder (small black arrow) is normal.

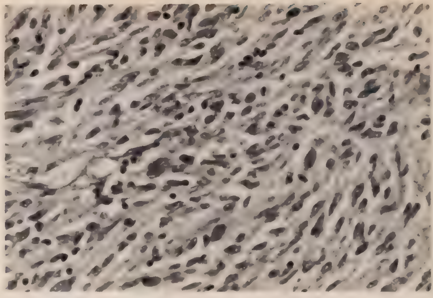

FIG. 3. Photomicrograph showing histological appearance of the tumor: spindle-form cells, some of them atypical with a few mitoses; H&E ×250.

During anesthesia, massive pulmonary aspiration occurred and the patient died of sepsis three days later. On postmortem examination, no remnants of the tumor and no metastasis were found.

Case 2. A 65-year-old white man, born in Poland, was admitted because of intermittent melena for one year. A barium meal and a hypotonic duodenography showed a small, well-delineated filling defect in the third part of the duodenum which appeared submucosal on duodenoscopy. Biopsy revealed normal mucosa. Considering the small size of the apparently benign tumor and its location, the patient was followed up for a few months, during which the radiological finding remained unchanged. Finally, the patient was operated on because of persistent decrease of the

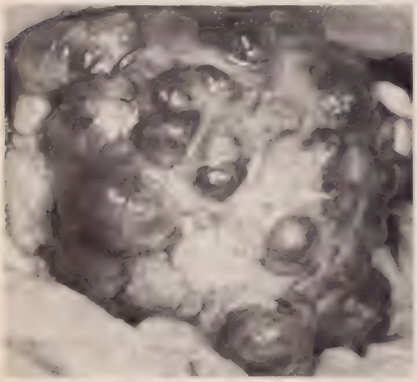

FIG. 2. Case 1. The anterior surface of the tumor, which is exophytic.

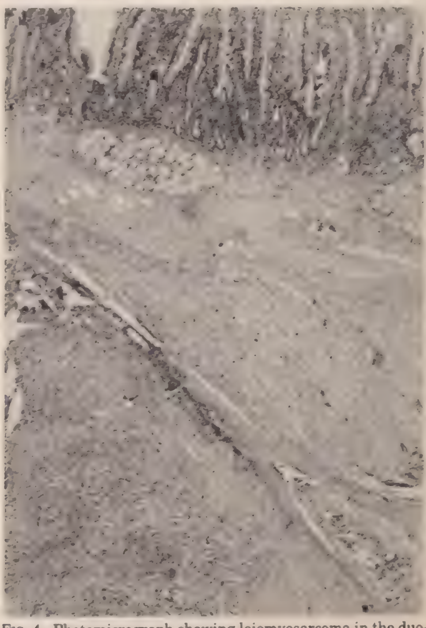

FIG. 4. Photomicrograph showing leiomyosarcoma in the duodenal wall, covered by normal mucosa; H&E ×40.

hemoglobin level. The tumor was completely removed by resection of the third part of the duodenum with end-to-end anastomosis (Fig. 5). Recovery was uneventful. The resected specimen consisted of a 4 cm long segment of the duodenum. A multinodular mass protruded to the luminal as well as to the serosal aspects of the duodenal wall. The mass appeared to be confined to the intestinal wall and covered by serosa. The duodenal mucosa above the mass was ulcerated centrally. The cut surface showed whitish-gray fibrillar tissue of fine rubbery consistency with areas of calcification. Histologic diagnosis was leiomyosarcoma.

Discussion

Leiomyosarcoma is a rare primary malignant duodenal tumor, twelve times less frequent than adenocarcinoma (2). The incidence of this tumor is equal in both sexes. The ages of the patients vary between 21 and 80, with a peak incidence between 40 and 49, that is, one decade earlier than the peak incidence of adenocarcinoma. There is only one pediatric case in the literature (9).

These tumors may arise from the smooth muscle of the muscularis mucosae or muscularis propria, from isolated scattered muscle fibers in the subserosa, or, perhaps, from blood vessel walls (10). In the great majority of the cases the tumor is localized in the second part of the duodenum. There is a similar preponderance of duodenal adenocarcinomas in this area. The tumor consists of lobulated, grayish-pink masses that may undergo ulceration, cavitation, hemorrhage, infection, calcification and perforation (11). Sometimes it discharges purulent mucus into the bowel. There is no agreement among authors concerning the existence of a capsule. The size of the tumor may vary from 2–5 cm in diameter to the size of a child's head, the mean size being 7.5 cm in diameter. Microscopically, the tumor consists of interlacing bundles of spindle-shaped or pleomorphic cells with hyperchromatic nuclei often arranged in palisades with infiltration to local tissues. The diagnosis of malignancy is based on the increased cellularity of the tumor, the presence of occasional multinucleated giant tumor cells, atypia, and increased frequency of mitosis. Nevertheless, some authors do not believe that the number of mitoses reflects malignancy of this kind of tumor (12).

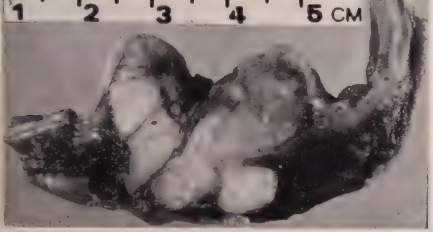

FIG. 5. Case 2. Gross appearance of the cut surface of the duodenal tumor. The mucosal surface above the mass is ulcerated.

The principal symptoms are weakness, weight loss, abdominal pain, vomiting, dyspepsia, fainting, respiratory distress, and malaise. The common signs are anemia, melena, palpable abdominal mass, hematemesis, jaundice, intestinal obstruction, swelling of the leg, and fever. Less common signs include obstructive uropathy, tachycardia, and acute abdomen due to perforation.

Radiologically, the most characteristic abnormality on a barium meal is a submucosal filling defect with central ulceration or fistula formation into the retroperitoneal space or into other viscera (13). In one third of the cases, the gastrointestinal series is normal because of outward growth of the tumor (toward the serosa). On barium enema, extraluminal defects may be detected in half of the cases. Arteriography allows a more specific differential diagnosis, since the leiomyosarcoma exhibits hypervascularity with irregular vessels and venous lakes in the tumor bed. With extensive hemorrhagic necrosis, there may be no tumor vascularity demonstrable (14). To our knowledge, this is the first time ultrasonography was done for leiomyosarcoma of the duodenum, but echographic images have proved to be a good diagnostic tool in intramural tumors of the gastrointestinal tract (15).

This tumor spreads mainly by local infiltration and vascular embolization. Lymphatic spread is less common. Metastases were found in liver, gallbladder, lymph nodes, and peritoneum; more rarely in the mesentery, omentum, and spine; and, in a single instance, in the lungs (16).

The best treatment is local removal of the tumor with the regional lymph nodes. When the tumor develops in the first, third, or fourth part of the duodenum, a radical resection is relatively easy to perform. When it develops in the second part, some authors advise a pancreatoduodenectomy as the treatment of choice (2). The size of the tumor should not deter the surgeon during the operation. Some great tumors have been removed with good surgical results (17). Frozen section is not advisable, since differentiation between leiomyoma and leiomyosarcoma may be impossible by this technique. Preoperative radiotherapy has been considered of no benefit by most authors, yet two cases have been reported in which the tumors were significantly reduced in size by preoperative radiotherapy (2, 17).

The longest survival period reported is seven years and five months. The average followup is about eighteen months, but several patients lived for as long as two years.

There is no good correlation between gross and pathological appearance of gastrointestinal smooth muscle tumors, their signs and symptoms, and the prediction of clinical outcome. As Weinstein and Roberts (18) note: "the high and early mortality is not due primarily to the unusually malignant nature of the tumor, since it is slow-growing. The answer may be found to be the location of the tumor in the duodenum, an anatomical region difficult to operate in and well known for its many post-operative complications. The frequent breaking down of the duodenal anastomoses and duodenal and pancreatic fistulization caused many early post-operative deaths."

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Submitted for publication September 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

A Case of Bilateral Dermoid Cysts, Insulin Resistance, and Polycystic Ovarian Disease: Association of Ovarian Tumors with Polycystic Ovaries with Review of the Literature

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Abstract

A case of a 16-year-old girl with hirsutism and oligomenorrhea who developed a pelvic mass is described. No acanthosis nigricans or increased androgen was noted in our patient, but insulin resistance was present. Laparotomy revealed bilateral dermoid cysts with polycystic changes of the ovaries. No histopathologic evidence of stromal luteinization in the tumors or in the surrounding ovarian tissue emerged. Only one previous case report describes ovarian disease (PCOD) with bilateral dermoid cysts of the ovaries. Patients with polycystic ovaries are at risk for the development of ovarian tumors. A review of the literature reveals 68 additional cases of ovarian tumors with PCOD.

Polycystic ovarian disease (PCOD) has been reported in association with congenital adrenal hyperplasia (1–3), androgen-producing tumors of the adrenal (4, 5), pituitary tumors (6–9), and a variety of ovarian neoplasms (10–28). Among the latter group, dermoid cysts have been described in patients with PCOD (10, 13, 17, 18). Hirsutism with dermoid cysts of the ovaries has also been reported without associated polycystic changes of the ovaries (29–34). Feminization in association with a dermoid cyst of the ovary has also been described (35). The finding, however, of bilateral dermoid cysts of the ovaries in association with polycystic ovaries is extremely rare and has only been reported previously by Imperato-McGinley et al (18). It is the purpose of this communication to report another case of bilateral dermoid cysts found in an insulin-resistant patient with polycystic ovarian disease and normal androgen levels, and to stress the importance of excluding associated ovarian neoplasms in this syndrome.

Case Report

A 16½-year-old white girl was first seen for increasing hirsutism and acne of 4 months' duration. She reported menarche at the age of 15½ years, followed by menstruation at regular intervals of 28 days lasting for 4 days. The patient reported excessive facial hair since she was 13, recently progressive over the trunk and extremities. She had noted intermittent abdominal pains, mainly in the lower right abdomen, particularly prior to menses. Her last menstrual cycle occurred 5 months prior to evaluation and was painless. She reported no headaches, galactorrhea, lethargy, polydypsia, scalp hair loss, or deepening of her voice. Her family history revealed that two older brothers were diagnosed as having delayed puberty, but had developed normally with no endocrine deficits.

Physical examination revealed a clinically euthyroid girl of 65 inches, weighing 145½ pounds. Her blood pressure was 116/80 mm Hg. Moderate

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facial hirsutism was present over the face and intermammary areas. There was a male-pattern pubic hair distribution. The breasts were normally developed with no discharge or palpable masses. No acanthosis nigricans was present. Pelvic examination revealed a normal-sized clitoris. The uterus was of normal size, axial in position, and pushed to the left. A mass with a doughy consistency was palpable on rectal examination. Complete blood count, urinalysis, and blood chemistry findings were all within normal limits. Endocrine studies are summarized in Table I.

Pelvic ultrasonography revealed a 4.2 cm cystic lesion superior to the uterus in the right side of the pelvis. Another 6.0 cm lesion medial to this lesion yielded strong echoes in its inferior half and was echo-free superiorly. The uterus was normal in size and shape. On exploratory laparotomy July 9, 1981, both ovaries were enlarged and appeared cystic. The right ovary was the size of a small orange and had a large solid portion posteriorly which was shelled out of the ovary; a frozen section yielded the report of a dermoid cyst. The remainder of the ovary was reconstituted and retained its multicystic appearance. On inspection the left ovary was enlarged to the size of a hen's egg; one portion appeared to contain sebaceous material. Cystectomy was performed, and the intact cyst was reported histologically as a dermoid cyst. The ovary was reconstituted and was also multicystic. Numerous dilated subcapsular follicular cysts as well as atretic follicles were present beneath the thickened white fibrotic capsules covering both ovaries.

The specimen labeled "right ovarian tumor" weighed 65 gm and measured 7 × 6 × 4 cm, consisted mainly of a cystic tumor of 4 × 4 × 3 cm, and contained greasy yellow-white material admixed with deeply pigmented hairs. An elevated, firm 1.0 × 0.5 cm portion of tissue protruded into the cyst cavity. The ovarian capsule was thickened and semi-opaque and measured 0.1 cm. Immediately under the capsule, multiple cystic structures measuring 0.7–1.1 cm were visible. Microscopically, the greater part of the dermoid cyst was lined by keratinizing squamous epithelium. Skin appendages, cartilage, bone, and thyroid tissue with colloid-filled follicles were also present. The ovarian capsule consisted of a dense eosinophilic fibrous tunica albuginea which overlay stroma containing follicles in varying stages of maturation and resolution. The theca interna cells and ovarian stroma did not appear luteinized.

The specimen labeled "left ovarian tumor" weighed 21 gm and measured 5 × 3 × 3 cm. It consisted of a multiloculated cystic mass without visible overlying ovarian capsule or stroma. The cyst contained deeply pigmented hairs and thick material similar to that in the right ovary specimen. Microscopically the sections showed a dermoid cyst similar to the cyst in the right ovary with only a small amount of ovarian tissue.

The patient was reevaluated August 17, 1981, at which time she was well and had a normal menstrual cycle. Postoperative endocrine studies are summarized in Table II. The results of a glucose tolerance test with serum insulin levels performed September 4, 1981 is shown in Table III.

TABLE I

Preoperative Endocrine Studies

Serum	
T4-RIA	9.6 μg/dl
TSH	4.5 μU/ml
LH	28.0 mIU/ml
FSH	5.6 mIU/ml
Testosterone	46.0 ng/dl (normal, female, 30–85 ng/dl)
% Free Testosterone	1.8% (normal, female, 0.5–1.8%)
Free Testosterone	8.3 ng/ml (normal, female, 1.5–9.0)
Prolactin	16.0 ng/ml (normal, female, 5–20 ng/ml)
Beta subunit, HCG	<10.0 mIU/ml
Dehydroepiandrosterone sulfate (DHA-S)	216.0 μg/dl (normal, female, 82–338 μg/dl)
Urine	
24-hr. total 17-ketosteroids	21.1 mg/24 hr
24-hr. 17-hydroxycorticoids	6.8 mg/24 hr

TABLE II

Postoperative Endocrine Studies, Serum

LH	5.2 mIU/ml
FSH	6.9 mIU/ml
Testosterone	47.0 ng/dl
Prolactin	10.5 ng/ml
DHA-S	370.0 μg/dl
Androstenedione	175.0 ng/dl (normal, female, 60–300)
Insulin	59.9 μU/ml (normal, 5–20 μU/ml)

Glucose tolerance was normal. Both basal and glucose-stimulated hyperinsulinemia occurred with fasting serum insulin at 43.9 μU/ml (normal, 5–20 μU/ml) and peak insulin levels of 364–368 μU/ml from 60 to 120 minutes (normal, up to 100 μU/ml) (36). Titers of serum antireceptor antibody (courtesy of Dr. Jeffrey S. Flier, Beth Israel Hospital, Boston, MA) were negative (37). The level of basal serum proinsulin (courtesy of Dr. Arthur H. Rubenstein, University of Chicago School of Medicine, Chicago, IL) prior to the 75-gm glucose load were 3% (normal range, 5%–22%) (38).

Discussion

The patient in this report had oligomenorrhea, hirsutism, absence of clitoromegaly, normal breast development, and an increased serum LH/FSH ratio. These features are frequently encountered in patients with polycystic ovarian disease (PCOD) (39). In view of complaints of abdominal discomfort and the presence of a palpable pelvic mass, an ultrasound examination of the pelvis revealed findings suggestive of a dermoid cyst. At laparotomy, bilateral dermoid cysts were noted in association with polycystic ovaries.

It is of clinical importance to make a definitive diagnosis of PCOD in view of several important associations: (a) endometrial hyperplasia and development of carcinoma of the uterus in a relatively young age group (40–44) and (b) an incidence of ovarian tumors reported to range from 4.6% to 17.0% (10, 17). A unique and frequently encountered clinical finding in PCOD is the increased LH/FSH ratio, which should be sought with repeated pooled sera to exclude fluctuations of serum LH in these patients. The pathophysiology of this finding and other hormonal data are adequately summarized in a review of PCOD by Goldzieher (39).

Of the many types of ovarian neoplasms associated with PCOD (Table IV), the most commonly found are dermoid cysts (10, 11, 13, 17, 18). Ovarian dermoid cysts constitute 24 of the 69 cases (35%) of ovarian tumors reported with polycystic ovaries. Only one other case of bilateral dermoid cysts associated with PCOD has been described, by Imperato-McGinley et al (18). In that report a 15½-year-old girl with hirsutism, primary amenorrhea, acanthosis nigricans, and insulin resistance was described. Preoperatively, serum testosterone and Δ-4-androstenedione levels were elevated. Following removal of the dermoid cysts and wedge resection of the ovaries, menses and serum androgens normalized and the acanthosis

TABLE III

Glucose Tolerance Test Results (75-gm glucose load)

Minutes	Serum glucose mg/dl	Serum insulin (μU/ml)
0	78	43.9
30	155	220.0
60	160	364.0
90	128	360.0
120	140	368.0
180	50	53.6
240	75	—

TABLE IV

*Polycystic Ovaries and Coexisting Ovarian Tumors**

	# pts	References
Dermoid cysts	24	10, 11, 13, 17, 18, present case
Arrhenoblastomas	8	12, 14, 17, 20, 21, 24, 26
Thecomas	5	10, 15, 16, 23
Papillary fibromas and papillomas	5	17
Cystic granulosa cell tumors	4	17, 22
Adrenal rest tumors (lipid cell)	4	10, 12, 17
Hilar cell tumors	4	17, 27, 28
Papillary cystadenomas	3	17, 19
Pseudomucinous cystadenomas	2	17
Adenofibromas	2	10
Dysgerminoma	1	10
Serous cystadenocarcinoma	1	10
Bilateral mucinous cystadenoma	1	11
Serous cystadenoma	1	11
Hemorrhagic cyst (?type)	1	11
Mesonephroma (clear cell tumor)	1	17
Interstitial cell tumor	1	12
Gynandroblastoma	1	25
TOTAL	69	

* No tumor classification attempted.

nigricans improved. In only two other detailed descriptions of patients with coexisting ovarian dermoid cysts and polycystic ovaries did regular menses resume following surgery (10, 13).

Two syndromes have been described in which marked insulin resistance is associated with acanthosis nigricans (37, 45). In Type B syndrome, which is an autoimmune disease, circulating insulin antireceptor antibodies are present. Our nonobese patient did not have Type B syndrome, since neither acanthosis nigricans nor antireceptor antibodies were present. In the Type A syndrome, the insulin resistance usually occurs with virilization, primary amenorrhea, and polycystic ovaries (45). The case reported by Imperato-McGinley and associates (18) is similar to a typical Type A pattern except that studies of the patient's monocytes revealed normal binding of ^{125}I-insulin to the cells. The patient described here also does not fit the Type A syndrome in view of the absence of acanthosis nigricans and lack of virilization or elevated androgen levels. Although hyperandrogenism and hyperinsulinism have been closely correlated in obese women with polycystic ovarian disease (46), our patient's insulin resistance is out of proportion to the normal serum testosterone and androstenedione levels. The precise mechanism of the insulin resistance in our patient with polycystic ovarian disease without obesity remains to be clarified.

Hirsutism has also been described in cases of ovarian dermoids without polycystic changes (29–34). The pathophysiology of increased androgen production in these patients is unclear, but the presence of luteinized cells in the tumor itself (31, 32) or in ovarian tissue surrounding the dermoid cyst suggests that these cells may initiate androgen or estrogen secretion (29, 31–34). Neither for the hirsute amenorrheic patient of Imperato-McGinley (18) nor for the patient in this report was stromal luteinization in the bilateral dermoid cysts or in the surrounding polycystic ovarian tissue demonstrated. Although the incidence of endocrine dysfunction with dermoid cysts is infrequent (47), normalization of menstrual dysfunction (menorrhagia, oligomenorrhea) following excision of the dermoid cyst has been described (32, 48–50). An isolated report of feminization in an elderly woman (35) and isosexual precocity in a 4-year-old girl (11) has also been described. Stromal luteinization associated with virilization has also been described in various other ovarian tumors, both benign and malignant, primary or metastatic (33, 51). The mechanism of these changes is poorly understood.

In conclusion: this report stresses the importance of frequent follow-up examinations of patients suspected of PCOD. The development of an associated ovarian neoplasm should be considered in such a patient who develops a pelvic mass or whose endocrine state indicates more rapid virilization or amenorrhea. Since direct visualization by laparoscopy may not always reveal small ovarian tumors, laparotomy is indicated after careful clinical evaluation. Furthermore, the development of virilization, amenorrhea, menorrhagia, reduction of serum LH, and hyperprolactinemia should also alert the physician to etiologies other than ovarian tumors—for example pituitary tumors (7, 9) and endometrial carcinoma (41, 43).

Acknowledgments

We are grateful for the technical assistance of Maria T. LaRaque and to Marva D. Wiliams for her secretarial help.

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Submitted for publication September 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Treatment of Refractory Ascites in Hemodialysis Patient with Peritoneovenous Shunt (Denver Shunt)

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Abstract

Ascites in hemodialysis population is a recognized clinical entity whose pathophysiology and treatment have not been definitely established. Nephrectomy, transplantation, fluid intake restriction, and peritoneovenous shunt have been tried with variable success. A case of hemodialysis-associated ascites in which successful treatment was obtained with insertion of a peritoneovenous shunt (Denver shunt) is reported.

Case Report. The patient is a 42-year-old woman who underwent a hysterectomy in 1975 for fibroid myoma. In 1977, lupus erythematosus was diagnosed. Deterioration of kidney function progressed during the following three years, and peritoneal dialysis was started in December 1979. Vascular access was also constructed at that time. In January 1980 the peritoneal catheter was removed and the patient was placed on maintenance hemodialysis (HD) three times a week. Her weight at that time was 170 pounds. In June 1980 she began to gain weight and noticed an increase in abdominal girth; by August 1980, she weighed 180 pounds. All attempts to remove fluid while she was undergoing hemodialysis were unsuccessful. The patient then underwent an extensive evaluation for massive ascites, including multiple cultures of the fluid and minilaparotomy with peritoneal and liver biopsies. No cause for the ascites could be found, while abdominal girth continued to increase. Because the symptoms became worse and the patient developed orthopnea, in October 1980 cardiac catheterization was performed. This procedure strongly suggested the diagnosis of constrictive pericarditis, and no other cause of cardiac ascites could be found. A pericardiectomy failed to relieve the ascites. By November 1981, the patient weighed 184 pounds, and the ascites and dyspnea had progressively increased. The patient was admitted to the hospital; fluid intake was closely monitored, and further attempts at reducing intravascular volume did not relieve the ascites. A Denver shunt was then inserted by the standard procedure while the patient was under general anesthesia (Fig. 1). While the patient was on HD, the ascites was reinfused by flat decubitus and manipulation of the pumping device of the Denver shunt. In two weeks, the abdominal girth returned to normal, and the patient's weight decreased to 150 pounds with concomitant disappearance of orthopnea. After ten months of follow-up, patient is free of ascites.

Discussion. Intractable, massive ascites in patients with end-stage renal disease on maintenance hemodialysis is infrequent. The clinical picture has been well described despite the small number of collected cases from different centers (1, 2). The etiology is still not well understood and different therapeutic approaches have been tried

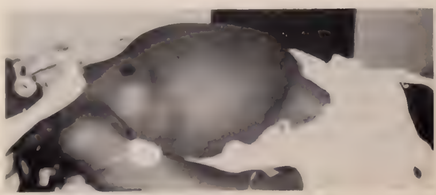

FIG. 1. Patient at insertion of Denver shunt. Massive ascites interferes with ventilation.

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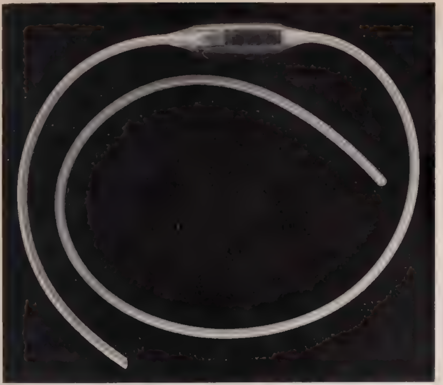

FIG. 2. Denver shunt. Distal part with fenestrations is placed in peritoneal cavity. Pump-valve mechanism is placed subcutaneously over lower anterior chest wall; proximal part of tube ascends subcutaneously toward neck, where it enters internal jugular vein.

with variable results (3, 6). This condition is generally refractory to fluid restriction or intensive hemodialysis (5). Compartmentalization of fluid or decreased water and electrolyte exchange by the peritoneal membrane seems the most plausible explanation (6). Treatment of ascites by peritoneovenous shunt (P-V shunt) has become common for patients with refractory ascites related to liver or neoplastic disease (7). In these cases, the fluid reinfused in the circulation is eliminated by increased diuresis. In patients being treated by hemodialysis, the fluid can be removed only during the dialysis. Currently, two different types of P-V shunt are used. The Leveen shunt consists of a silastic tube and an interposed one-way pressure-activated valve. The Denver shunt is a similar device additionally equipped with a pressure-operated one-way valve and a pumping mechanism which can be activated by external, repetitive compression (Fig. 2). This feature has allowed our patient to selectively reinfuse the ascitic fluid while on dialysis, minimizing the risk of fluid overload. The patient is well and free of ascites 10 months after the procedure. This result should encourage further trial of this mode of treatment.

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Submitted for publication September 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Transportal Blood Sampling for Preoperative Localization of Insulinomas

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Abstract

After diagnosis of an insulinoma, preoperative localization of the tumor is of great help to the surgeon. Angiography, the most widely used method, has been successful in 40% to 88% of cases. More recently, tumors have been localized by demonstration of a step-up of insulin levels in blood obtained by transportal sampling of the portal and pancreatic veins. Five cases with documented insulinomas and negative angiography and a sixth case with a positive angiogram are described. The tumor was successfully localized by transportal sampling in all six cases. A seventh case is reported in which positive angiographic and CT scan localization was questioned preoperatively because transportal venous sampling did not reveal insulin step-up in the presumed site of the tumor; incomplete portal-vein sampling did not include the area draining the tumor discovered during surgery. The need for subselective pancreatic vein sampling was evident in at least two cases. Transportal blood sampling is a reliable technique which can be used for the localization of all hormone-secreting tumors of the pancreas, including gastrinomas, glucagonomas, and tumors secreting vasoactive intestinal polypeptide.

Pancreatic arteriography, the most widely used method for localization of insulinomas, is successful in 60% of cases (range 40% to 88%) (1–3). Even subtraction techniques and subselective studies have failed to localize all the tumors (3). The great variability in accuracy judged by reports from a number of major medical centers may relate to the location of the tumors, use of subtraction and subselective examination, or reporting of postoperative retrospective tumor localization rather than preoperative findings. Recently, several groups have described a method of localizing insulinomas by demonstration of a step-up in insulin levels in blood obtained via transhepatic venous catheterization of the pancreas (4–8). We now report a series of seven patients with diagnostically proven insulinomas; preoperative tumor localization was achieved in six by transhepatic venous sampling. In the seventh patient, preoperative portal vein sampling showed a discrepancy with later documented false-positive radiographic studies.

Methods

The seven patients reported on here were evaluated for the presence of an insulinoma at The Mount Sinai Medical Center between 1977 and 1982. Initially all patients had symptoms of neuroglycopenia (summarized in Table I). Diagnostic evaluation included a three-day fast with sequential glucose and insulin levels, yielding positive findings in all seven patients. Methods for localization of the tumors (Table II) included celiac angiography (n = 7), sonography (n = 5), abdominal CT scan (n = 4), and transhepatic portal vein catheterization (n = 7). During the transhepatic portal vein catheterization in patients D and E,

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This work was supported in part by NIH grants AM18522 and RCDA KO4 AM00089 (Dr. Rayfield), an anonymous donor in honor of Dr. Gerald J. Friedman, New York, and by the KROC Foundation. Dr. Goldberg is supported by a Clinician Scientist Award from the American Heart Association and its local affiliate the New York Heart Association. Dr. Giegerich is supported by a Juvenile Diabetes Foundation Research Fellowship.

Presented in part at a meeting of the New York Surgical Society, Feburary 10, 1982.

TABLE I
Clinical Features of Insulinoma Patients

Patient	Sex	Age	Symptoms	Duration of Symptoms Prior to Diagnosis
A	M	28	inappropriate behavior, diaphoresis, reddening of the face, loss of consciousness	2 mos.
B	M	43	leg heaviness, distant feeling, "looked and acted drunk"	3 mos.
C	M	68	diplopia, acute confusional state	6 mos.
D	F	56	lethargy, confusion, loss of memory	18 mos.
E	M	42	transient memory loss, slurred speech, diaphoresis, decreased concentration	6 years
F	F	58	nocturnal tonic clonic movements with urinary incontinence, loss of consciousness	6 mos.
G	M	43	confusion, unsteady gait, difficulty concentrating, loss of consciousness	8 mos.

samples at 5 sites were obtained, whereas in patients A, B, C, F, and G, a greater number of subselective samples were obtained from smaller pancreatic veins.

Results

As noted in Table I, 5 patients (A-E) had negative pancreatic angiography. CT scan and sonography were useful in only one of the cases (G). However, preoperative localization by transhepatic venous catheterization was successful in all 5 of the patients with negative angiography and in 1 additional patient (G) with a positive angiogram. Figure 1 shows the venous insulin levels obtained from these studies and the location of the 6 tumors at surgery. Localization was accomplished by this method whether the tumor was in the head, neck, or tail of the pancreas.

Patient F was preoperatively presumed to have

TABLE II
Diagnostic Criteria and Methods of Tumor Localization

Patient	Fast Immunoreactive Insulin (μU/ml)/Lowest Glucose (mg/dl)	Sonography	CT Scan	Angiography	Portal Vein Catheterization	Tumor Size/Location at Surgery
A	69/40	—	ND	—	+	2.5 cm distal pancreas
B	11/38	ND	ND	—	+	2 cm junction of body and tail
C	57/36	—	—	—	+	4 × 7 × 9 mm head
D	17/23	ND	—	—	+	7 mm neck
E	50/32	—	ND	—	+	1.5 cm head
F	16/32	—	FP	FP	Inc	1 cm head
G	44/25	+	+	+	+	1.5 × 1.8 cm junction of body and tail

+ = positive; − = negative; Inc = incomplete; ND = not done; FP = false positive.

a lesion at the junction of the body and tail by CT scan, angiogram, and portal vein venogram (Table II, F). The preoperative transhepatic venous catheterization failed to reveal a step-up of insulin secretion from the area in question (Fig. 1, F). At operation, no lesion was palpated in the body or tail corresponding to the area noted by radiographic study. A 1 cm adenoma was identified in the head of the pancreas, and no recurrence of hypoglycemia was noted after a 72-hour postoperative fast. Review of the radiographic studies after the operation indicated tortuosity of the splenic vein and possible pseudotumor due to compression of the tissue in the body-tail junction. The venous sampling was correct in indicating no tumor in the area in question but was an incomplete study because samples were not obtained from the venous drainage of the head of the pancreas.

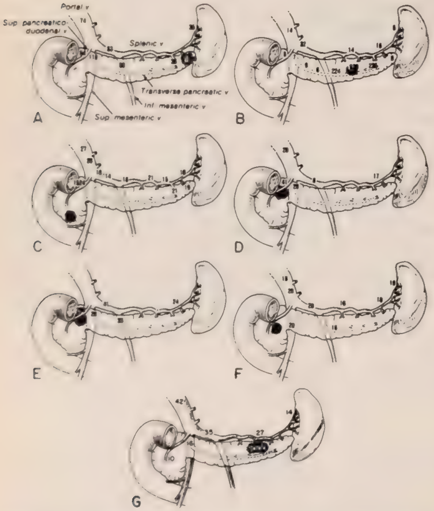

FIG. 1. Numbers indicate preoperative transportal insulin levels (μU/ml) in 7 patients identified by letter. Veins sampled are named in panel A. Black circle indicates location of tumor.

Discussion

The presence of an insulinoma should be suspected in patients exhibiting episodic hypoglycemia, especially in association with periods of fasting or exercise. Lack of normal suppression of the serum insulin levels is the most useful diagnostic test for this tumor. A prolonged fast for up to 72 hours yielded an insulin/glucose ratio of greater than 0.3 in 5 of our 7 patients, consistent with the diagnosis of insulinoma by the criteria of Fajans (9). An additional patient (B) had a diagnostic fast for insulinoma when the criterion of Turner (10), (100 × insulin)/(glucose-30) greater than 50, was used. A rapid and convenient suppression test which assays C-peptide release during exogenous insulin infusion has been useful in many cases (11) and may replace the fast as the initial diagnostic evaluation. Although an occasional patient with a beta-cell adenoma will suppress C-peptide to normal levels during insulin infusion, such a response is unusual (12). Stimulation tests showing an exaggerated insulin response to tolbutamide, glucagon, leucine, or calcium along with a prolonged hypoglycemic phase may also be useful if the diagnosis is in question (13).

The lack of a reliable method for accurate preoperative localization of insulinoma in patients with positive diagnostic studies may contribute to the operative morbidity and technical problems associated with removal of these tumors. Currently, 15% to 30% of patients with insulinomas undergo reoperation (14) and an undertermined number require more extensive pancreatic resections for the surgeon to remove the entire tumor with confidence (15). Although pancreatic arteriography is the most widely used method for localization of these tumors, once metabolic studies point to such a diagnosis, this technique has a number of shortcomings. The reported 12% to 60% incidence of false negative studies may result in part from difficulty visualizing tumors less than 1 cm in diameter (16). Furthermore, the angiographic tumor blush from an insulinoma located in the tail of the pancreas may be obscured by the hypervascularity of the spleen. In addition, the 13% incidence of multiple tumors (16) compounds these difficulties. Hence, angiographic localization and removal of one tumor may be insufficient therapy for some patients. An occasional patient may initially present symptoms that seem to resemble an insulinoma, but without a tumor (13). These patients with diffuse hyperplasia of the beta cells cannot be differentiated from the 40% of patients with insulinomas and negative arteriograms. Transhepatic portal vein sampling has successfully been used to identify such patients (8).

Recently, occasional insulinomas have been localized by the finding of a local step-up of serum insulin levels from blood obtained via transhepatic catheterization of the portal and splenic veins (4-8). Of the seven cases we now report, 5 had a negative pancreatic arteriogram prior to transhepatic catheterization. Blood sampling in our chronologically first two patients, D and E (7), was restricted to the portal and splenic veins. Thereafter, subselective sampling from the pancreatic veins was performed. As can be noted from Figure 1, the localization of the tumor in patients B and G would have been missed had subselective sampling not been done. Due to the variability of the pancreatic venous drainage (17), an initial celiac angiogram is recommended to visualize the major veins prior to subselective sampling.

In three of the patients (C, E, and G), transportal venous localization was useful to the operating surgeon. In patient E, the tumor was located in an area of the head of the pancreas obscured by overlying duodenum and thus was difficult to palpate at surgery. In patient A, the high insulin level in the distal splenic vein should have easily identified that tumor, but the additional finding of a step-up of insulin in the superior mesenteric vein was confusing. A portion of the drainage of the tail of the pancreas may be via the transverse pancreatic vein into the superior mesenteric vein. This should be kept in mind in interpreting an insulin step-up in the superior mesenteric vein and explains this finding in our patient. Patients B and D had tumors that were easily palpable to the operating surgeon. Patient F is of interest because she represents a case of false-positive radiographic localization. Despite the incomplete portal vein sampling procedure which did not sample the area draining the tumor found in the head at surgery, the surgeon did not need to blindly resect distal pancreas and spleen for a nonpalpable lesion because venous samples from this area did not reveal an insulin step-up. Postoperatively no patient has had a recurrence of symptomatic hypoglycemia.

Transhepatic portal catheterization was associated with some local pain during the procedure but no major complications requiring an extension of hospitalization. This procedure was unsuccessfully attempted in one additional patient. Angiographic findings for this patient were positive; the patient was very obese, and after a single attempt to find a portal vein radical failed, the patient refused a second attempt.

Thus, insulin measurements obtained from venous sampling of the pancreas successfully localized 6 insulinomas and brought into question preoperative radiographic localization in a seventh patient. In 3 patients this information was useful to the operating surgeon. Our data and those of Glaser et al (8) indicate that subselective sampling and knowledge of the pancreatic venous drainage are needed to accurately localize some tumors. In view of these findings, the radiologic evaluation of a patient with hyperinsulinism and a negative arteriogram is incomplete without transportal venous sampling. Since even positive arteriographic localization of a tumor may be misleading, it seems reasonable to perform this procedure prior to surgery despite arteriographic results. As indicated by Patient F, care must be taken to systematically sample as many subselective pancreatic veins as possible from the entire pancreas without excluding a region of the pancreas based on prior radiographic studies, since false positive arteriographic studies occur. In view of the 13% incidence of multiple adenomas that are smaller than the limits of detection by angiography or CT scan, efforts should be made to sample the entire pancreas. We fully expect that additional patients will be found to have negative portal vein catheterization studies, since sampling of subselective veins draining the adenomas may not be technically possible. Furthermore, there is evidence that this technique is useful for localizing other hormone-secreting tumors of the pancreas, such as gastrinomas, glucagonomas, and tumors secreting vasoactive intestinal polypeptide (8, 18).

Acknowledgments

We would like to thank Drs. L. Gabrilove, D.A. Dreiling, J. Rudick, M. Luria, D. Bergman, and J. Chown for referring their patients for study.

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Submitted for publication October 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

External Choledochoduodenostomy: A Controversial Approach to Management of Choledocholithiasis

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Abstract

Ascending cholangitis, the sump or blind-sac syndrome, and alkaline reflux gastritis are drawbacks commonly ascribed to side-to-side choledochoduodenostomy. Many surgeons view this procedure as a last resort to be used only in elderly patients and in those whose common duct is wider than 15 mm. This report attempts to document the incidence and severity of the ascribed complications by retrospective analysis of personal experience with patients from 1973 to 1976 and a prospective study of cases from 1976 to 1981. In those years 61 of these operations were performed on 47 women and 14 men; 15 patients were under 50 years of age, 20 were over 70. Preoperative intravenous cholangiography was used to evaluate duct width, which was less than 15 mm in 20 patients (32%). One patient died immediately after the operation. Followup included clinical interviews and liver biochemistries every 6 months, and ERCP 12–18 months after surgery. The long-term results in the 60 survivors were excellent, 48; good, 8; fair, 3; poor, 1. The data indicate that when properly done, side-to-side choledochoduodenostomy is safe and effective even when performed on common ducts less than 15 mm. The complications ascribed to the operation were not observed during followup. The excellent long-term results in this series justifies a broadening of indications to younger patients and to common ducts wider than 10 mm.

Following the description by Riedel (1) in 1888 of choledochoduodenostomy for distal common duct obstructions, a number of reports from continental Europe advocated its use (2–4). Over the years, most surgeons, particularly the American and British, rejected the procedure for routine use because of concern for possible complications. Following Sander's report (5) in 1946, numerous communications (6–11) have indicated the value of choledochoduodenostomy but in general have advocated it only for extremely wide common ducts (15 mm), for elderly patients, and for patients whose predicted survival is short-term, a position supported by endoscopic reports of duodenogastric reflux of bile containing duodenal contents associated with severe gastritis, postulated to result from biliary intestinal anastomosis (12).

In 1976, encouraged by our initial results with side-to-side choledochoduodenostomy, we decided to investigate retrospectively and prospectively the safety and long-term results of the procedure in order to answer the following questions:

1. What is the incidence of the sump syndrome and of ascending cholangitis?
2. Is it safe to perform side-to-side choledochoduodenostomy on common ducts less than 15 mm wide?
3. Is significant impairment of liver function a late complication of the operation?
4. Is duodenogastric reflux and bile gastritis a consequence of the procedure?
5. Should side-to-side choledochoduodenostomy continue to be a procedure of last resort or should its indications be broadened?

Subjects and Methods

From January 1973 through December 1980, one of the authors (A.M.A.) performed 69 side-to-side choledochoduodenostomies. Of these, 7 bypassed malignant obstructions of the terminal common duct and 1 drained a biliary tree communicating with an infected hydatic cyst. The remaining 61 operations were performed for biliary lithiasis and constitute the cases reported here.

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Preoperative workup (13) included intravenous cholangiogram to outline the distal common duct, as well as endoscopic retrograde cholangic pancreatography (ERCP) to rule out morphologic changes in the periampullary area. Increasing opacity and opacity persisting beyond two hours after intravenous administration of the radiopaque dye, or persistent opacification of the common duct 10 minutes after sublingual administration of 0.6 mg nitroglycerine, were taken to indicate obstruction at the papilla. We have not found the radiocholangiomanometric techniques (14, 15) to be valuable in defining common-duct obstruction. In our experience (13), common-duct width is the crucial parameter in indicating whether permanent decompression of the biliary tree is necessary (13). Calibration of the common-duct diameter under physiologic conditions that is, interplay between the secretory pressure of bile flow at the hepatocyte level and the systolic and diastolic phases of sphincteric action, is mandatory. Artificial intraductal pressures induced during manual injection of contrast material during ERCP or operative cholangiography are unreliable. We therefore prefer to use common-duct width as the decisive parameter and measure its diameter by preoperative intravenous cholangiogram or by caliper at the operative field. In our experience, a duct wider than 10 mm implies functional or organic obstruction and requires permanent decompression, whether or not stones are found (13).

Figure 1 illustrates the critical features of the technique of a triangular side-to-side choledochoduodenostomy. Following a Kocher maneuver, dissection is carried down as low as possible between the common duct and duodenum, taking care to preserve the retropancreatic arterial arcade (17). The longitudinal duodenotomy should be between 2 and 3 cm in length and retroduodenal in position to prevent tension on the anastomosis. A single layer of fine (000 or 0000) absorbable sutures is used to construct the anastomosis (18).

The operative findings, morbidity, and mortality observed in the series are summarized in Tables I–IV.

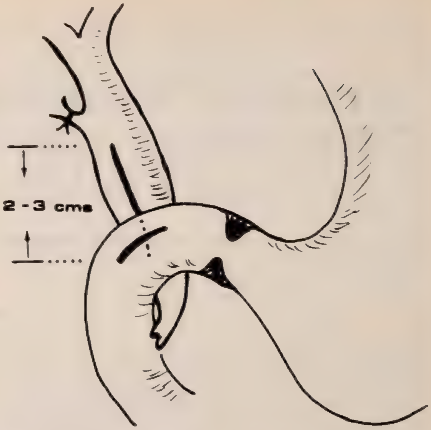

FIG. 1. Schematic drawing of the technique used in side-to-side choledochoduodenostomy.

Careful followup by independent clinical interviewers at 6–12 month intervals gathered information on the signs and symptoms of (a) cholangitis and hepatic dysfunction, including fatigability, fatty food intolerance, pruritus, colicky pains with chills and fever, urine or stool discoloration; (b) sump or blind-sac syndrome, including dyspepsia, diarrhea, steatorrhea, malnutrition; and (c) alkaline reflux gastritis and esophagitis, including heartburn, upper abdominal pain, anorexia, upper gastrointestinal bleeding, bile vomiting, weight loss. Peroral endoscopy and upper gastrointestinal x-rays were performed 12–18 months following surgery to determine (a) anastomotic patency and width, (b) the presence or absence of choledochal stones, (c) the presence or absence of duodenocholedal regurgitation and choledochal emptying, (d) duct and gastroduodenal mucosal inflammation, (e) the presence or absence of abnormal duodenogastric reflux.

The biochemical studies performed before operation and at 6–12 month intervals postoperatively were hematocrit and hemoglobin levels, serum iron, TIBC, transferrin, total serum pro-

TABLE I

Primary Surgery for Biliary Lithiasis and Associated Pathology (1/1973–12/1981)

Operation	No.	Operative morbidity	Operative mortality	Mean postop hospital stay
Cholecystectomy, simple	177	4 (2.3%)	1 (0.6%)	7 days
Cholecystectomy plus CBDE	68*	6 (8.8%)	1 (1.5%)	11 days
Total	245	10 (4.1%)	2 (0.8%)	9 days

* Stones actually detected in 51 (75%), overall rate 20.8%.

TABLE II
*Primary Choledochoduodenostomy for Biliary Lithiasis and Associated Pathology (1/1973–12/1981)**

Operation	No.	Operative Morbidity	Operative Mortality	Mean postop hospital days
Side-to-side choledochoduodenostomy	47	4	1	8
Sphincteroplasty	6	1	0	13
Y-loop hepaticojejunostomy	1	0	0	10
Choledocholithotomy, T-tube	14	0	0	13
TOTAL	68	5 (7.3%)	1 (1.5%)	11

* Choledochal stones 51; papillary stenosis 11; pancreatitis nodule 3; cholangitis 3.

teins, albumin and globulins, SGOT and SGPT, bilirubins, alkaline phosphatase, gammaglutamiltranspeptidase, prothrombin time, serum amylase, urinary bile pigments; intravenous cholangiography, endoscopic retrograde cholangiopancreatography.

At the end of one year, complete follow-up data was available on 43 of the 60 patients (75%), and at the end of two years, data was obtained from 26 patients (46%).

All patients in the series were operated upon by one surgeon (A.M.A.), rendering criteria and technique uniform; all endoscopic studies were performed by the same gastroenterologist (A.G.C.); and all interviews and interpretation of biochemical data were performed by independent observers.

Results

There was one hospital death among the 61 patients (1.6%). This occurred from massive upper gastrointestinal hemorrhage in a 74-year-old woman. Five other patients had postoperative complications (three minor and two major). One patient developed a superficial wound infection, another a minimal, temporary bile leak, and the third an episode of congestive heart failure responding rapidly to digoxin and diuretics. Major morbidity was encountered in two patients. The first developed an anastomotic cutaneous fistula draining over 500 ml/24 hr but it closed spontaneously after 3 weeks of total parenteral nutrition. The second major morbidity was generalized sepsis requiring intensive chemotherapy and prolonged hospitalization. Except for the two patients with major morbidities, the hospital stay was generally below 10 days and averaged 7 days following surgery.

The long-term results are summarized below. A widely patent oval or round anastomosis was observed in all of the 25 patients who underwent postoperative peroral endoscopy. No ductal nor duodenal mucosal changes were detected. No residual or re-formed stones were encountered, even in the two patients in whom all calculi could not be removed from the common duct at the time of bypass. In three patients food debris, that is, duodenal contents, were found lying in the terminal common duct but easily floating in and out through the choledochoduodenal stoma. Endoscopic evidence of abnormal duodenogastric reflux with gastritis confirmed by histologic biopsy was observed in three other patients.

Based on the data collected, a classification of the long-term results was elaborated:

Excellent (grade I): freedom from any symptoms even remotely related to the biliary or upper gastrointestinal tracts, to the operation, or to a complication of the anastomosis.
Good (grade II): presence of occasional minor gastrointestinal upsets, psychosomatic complaints, or wound complications.
Fair (grade III): continued significant digestive complaints, abnormal liver function.

TABLE III
*Reoperations for Biliary Lithiasis and Associated Pathology (1/1973–12/1981)**

Operation	No.	Operative Morbidity	Operative Mortality	Mean postop hospital days
Side-to-side choledochoduodenostomy	14	1	0	8
Sphincteroplasty	3	1	0	14
Y-loop hepaticojejunostomy	4	2	1	14
Choledocholithotomy, T-tube	1	0	0	12
TOTAL	22	4 (18.2%)	1 (4.5%)	12

* Residual stones 3; recurrent calculi 8; papillary stenosis 5; pancreatitis nodule 2; iatrogenic stenotic lesions (elsewhere) 4.

TABLE IV

Data on Side-to-Side Choledochoduodenostomy, Primary and Secondary Surgery (1/1973–12/1981)

No. of patients	61
Male	14
Female	47
Mean age (yrs)	60
<50 Yrs	15 (25%)
>70 Yrs	20 (33%)
Reoperations	14 (23%)*
Primary surgery	47 (77%)†
Duct width <15 mms	20 (33.0%)
Operative morbidity	5 (8.1%)
Operative mortality	1 (1.6%)
Mean postop. hosp. stay	7 days
Pancreatitis nodule	5 (8.1%)
Papillary stenosis	9 (14.7%)
Choledochal stones	47 (77.0%)

* Calculi detected in 8 of 14 (57%), classified as recurrent or primary (9, 16) in 7 of 8 (87.5%).

† Stones found in 39 of 47 (83%); in 5 of 39 the calculi, classified as primary (9, 16), could only be detected within the common bile duct.

Poor (grade IV): evidence of pathologic enterogastric reflux in patients with residual or recurrent stones, cholangitis, jaundice, or abnormal liver function requiring reoperation.

Using these criteria, 48 patients achieved an excellent result, 8 good, 3 fair, and 1 poor. All 3 of those classified as "fair" gave endoscopic evidence of alkaline reflux gastritis. The patient classed as "poor" had iatrogenic stenosis of the left hepatic duct at the hilum and submitted to an ill-advised choledochoduodenostomy, eventually corrected with a Y-loop hepaticojejunostomy.

Discussion

The morbidity and mortality (1.52%) observed in the present series is in agreement with and of the same order of magnitude as reports in the literature for choledochoduodenal anastomosis (2.4%–4.3%) (6–8, 10, 11, 19–21).

The data does not support the contention that biliary-duodenal bypass leads to hepatic dysfunction resulting from repeated bouts of cholangitis, nor were significant gastrointestinal complaints such as persistent diarrhea with nutritional impairment encountered. These complications, commonly described as the sump or blind-sac syndrome, presumably derive from stasis of bile and refluxed duodenal contents into the terminal common duct with bacterial overgrowth of anaerobes and other abnormal bacterial flora. The resulting cholangiolymphatic and cholangiovenous bacterial reflux, as well as the enhanced bile salt decomposition, result in the diarrhea and malnutrition observed in blind-loop syndrome arising elsewhere in the gastrointestinal tract (22–25). In the present series, only one patient developed repeated bouts of cholangitis requiring reoperation and bypass by Roux-en-Y hepaticojejunostomy. Another patient, two months following side-to-side choledochoduodenostomy, had recurrent severe episodes of diarrhea, which responded to oral metronidazole. Blind-sac syndrome can be avoided by wide anastomosis which prevents stasis, avoids the buildup of excessive common duct pressures (below 20 cm H_2O) (22), and permits the free flow of common duct contents, including duodenal reflux as well as calculi, back into the duodenum. Using the triangular technique (Figure 1) it is possible to construct a biliary duodenal anastomosis of sufficient diameter (15–20 mm) to prevent these complications even in a common duct of 10–15 mm. A widely patent and functional anastomosis is illustrated in Figure 2.

The possible long-term effect on liver function of loss of the odditic sphincter activity remains to be determined. Certainly there was no evidence in our study nor in reported clinical series of choledocholithotomy of impaired liver function (6–8, 10, 11). In the present series there was one patient whose severe liver dysfunction antedated the choledochoduodenostomy. Two other patients had transient slightly elevated levels of serum alkaline phosphatase.

Over the past 10 years considerable attention has been devoted to alkaline bile duodenogastric reflux resulting in alkaline or bile gastritis (26, 27), a complication originally described following Billroth I and II gastrectomy (28, 29), as well as cholecystogastrostomy, in which there is a continuous flow of bile directly or indirectly into the stomach due to neurohormonal motor dysfunction, loss of odditic sphincter (12), or anatomic reconstruction. In fact, continued discharge of bile into the duodenum occurs even after simple cholecystectomy, produces sphincter dysfunction, and has been reported to result in bile gastritis (30).

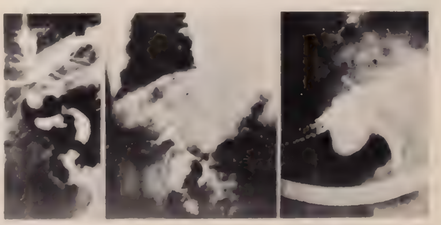

FIG. 2. Cholangiographic sequence before (**left**), during (**middle**), and 18 months after (**right**) operation on a patient whose common bile duct was 12 mm wide, as demonstrated during laparotomy.

In this series, abnormal duodenogastric reflux was observed in 3 of the 25 patients examined endoscopically. Two patients suffered no clinical complaint. The third patient's complaints and endoscopic abnormalities predated the choledochoduodenal anastomosis.

We believe the data in this series indicate that side-to-side choledochoduodenostomy is a safe procedure with low morbidity and mortality, that the operation is technically feasible and can be performed successfully in common ducts 10–15 mm in diameter, and that late complications of liver dysfunction, blind-sac syndrome, and abnormal duodenoduodenal reflux are low enough in incidence to warrant its use in patients with (a) common ducts wider than 10 mm, (b) recurrent common duct stones, and (c) benign pathology at the distal common duct. If proper technique is employed, that is, anastomosis wider than 20 mm, cholangitis and blind-sac syndrome are unlikely. There is no convincing evidence that choledochoduodenostomy results in abnormal duodenogastric reflux. Our experience leads us to conclude that the indications for the procedure should be broadened.

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Submitted for publication October 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A

Ulcerative Colitis and Hemophilia A

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Hemophilia A is a disease characterized by recurrent episodes of bleeding, primarily in deep soft tissue or joint spaces, due to a deficiency in levels of procoagulant activity of factor VIII. When a patient with hemophilia has a concomitant hemorrhagic disorder such as ulcerative colitis, the physician must assess which of the disorders is primary in causing a bleeding episode. We report a case of a patient with factor VIII deficiency who developed severe ulcerative colitis with major gastrointestinal bleeding.

Case Report. A 21-year-old male with classic hemophilia developed diarrhea characterized by more than five liquid, nonbloody stools per day in July 1981. In September 1981 his stool became bloody and was associated with tenesmus and a diffuse abdominal burning pain. Sigmoidoscopy revealed a friable mucosa consistent with ulcerative colitis. Stool for ova and parasites and cultures for enteric pathogens were negative. He was treated with prednisone 40 mg/day and Azulfidine 3 mg/day with little clinical improvement. A barium enema revealed disease in the left side of the colon. Three weeks prior to admission the patient noted increased frequency of stools; prednisone was increased without improvement. One week prior to admission he developed a fever of 101°F. On admission in October 1981 he complained of bloody bowel movements (5 to 10 per day), tenesmus, malaise, fever, and 20-lb weight loss over the preceding 3 months.

The patient's medical history was notable for hemophilia A which was documented at birth because of his family history. He underwent surgery at age two weeks for pyloric stenosis. The course of his hemophilia was generally mild without spontaneous bleeding. Major bleeding episodes occurred with circumcision performed at age 6 without factor coverage, and several muscle and joint space hematomata associated with trauma. He had baseline factor VIII levels of 3% to 4% and had no inhibitor. He was maintained on home care factor VIII administration and had last required therapy in August 1981 for hemarthrosis. There was no family history of inflammatory bowel disease.

Physical examination on admission revealed a well-developed, well-nourished male in mild distress. Vital signs were blood pressure 125/75 mmHg, pulse rate 80 supine; blood pressure 115/70, pulse rate 100 standing; temperature 100.8°F.HEENT exam, benign. Cardiac exam revealed: I/VI midsystolic flow murmur. Chest clear, normal bowel sounds and mild right upper quadrant abdominal tenderness without rigidity or rebound; skin and joints were normal. Laboratory studies revealed the following values: hemoglobin 15.2 gm/100 cc, white blood cell count 13,400/mm^3 with a left shift, platelets 190,000/mm^3, erythrocyte sedimentation rate 28 mm/hr, SMA 18 within normal limits. Stool Wright stain: multiple granulocytes. Stool culture for ova and parasites, *Salmonella, Shigella,* and *Campylobacter* sp.: negative (multiple samples). Counterimmunoelectrophoresis of serum for *Entamoeba:* negative.

The patient was begun on hydrocortisone 300 mg/day via continuous intravenous infusion without significant change in the number or consistency of his stools. His course was complicated by fever of 102° F without an evident source. He was treated with Cefoxitin and tobramycin with defervescence. On his fifth day in the hospital the patient passed large amounts of blood through the rectum, with marked orthostatic blood pressure drop, and he was treated with saline, transfusion

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Supported in part by Health Services Administration grant MCB-360001-04-01, Regional Comprehensive Hemophilia Diagnostic and Treatment Center and NHLBI Contract N01-HD-53020. The Margie Boas Fund, The Polly Annenberg Levee Hematology Center, Department of Medicine, Mount Sinai School of Medicine of The City University of New York, NY 10029.

of red cells, and factor VIII. Factor VIII infusion was continued at levels sufficient to maintain surgical hemostasis in order to separate the bleeding caused by hemophilia from the bleeding secondary to ulcerative colitis. On the thirteenth hospital day he hemorrhaged massively and continued to bleed heavily despite further factor infusion. Factor VIII levels were adequate and there was no evidence of an inhibitor. The patient required emergent total proctocolectomy which he underwent without complication.

Pathologic review of the colon revealed an edematous bowel denuded of mucosa from the rectum to the hepatic flexure. There was microscopic evidence of acute and chronic inflammation in the mucosa and submucosa with crypt abscesses.

Discussion. Hemophilia A is an X-linked, recessively inherited disease with an incidence of $1{:}10^4$ (1). Ulcerative colitis is an acquired disease with variable estimates of incidence ranging from 1.6–7.3 cases per 10^5 population (2, 3). This data yields a predicted estimate of the prevalence of ulcerative colitis in patients with classic hemophilia of approximately 4–8 per 10^8 population. This specific combination would therefore be a very rare occurrence. A literature search did not reveal any previous case reports of ulcerative colitis in a patient with hemophilia A.

One difficulty in managing a patient with hemophilia who develops inflammatory bowel disease is to determine if the patient is bleeding from deficient factor levels or the activity of the bowel pathology. Massive hemorrhage occurs in approximately 4% of patients with ulcerative colitis (2). In this patient we had maintained levels of factor VIII sufficient for hemostasis and continued maximal medical therapy for ulcerative colitis. Despite this, life-threatening bleeding occurred and the patient required surgery. This case demonstrates the critical need to overcome the coagulation defect in order to assess the activity of the underlying gastrointestinal disorder. In addition it shows that current technology allows uncomplicated major life-threatening surgery in patients with hemophilia (4).

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Submitted for publication November 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 3, May–June 1983
Printed in U.S.A.

Student's Corner

Barry Berson, B.A., Editor

Pheochromocytoma: A Clinical Study of the Role of Amines in the Development of Endocrine Dysfunction

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Abstract

Current literature suggests that biogenic amines act on peripheral endocrine tissue and on certain tumor tissues to augment the release of biologically active hormone (as opposed to immunologically active hormone). This is thought to occur by increasing the rate of posttranslational modification of the prohormone. The site of action of the amines is believed to be the amine, precursor, uptake, and decarboxylation system of cells. The present study asks if in Sipples syndrome (pheochromocytoma, medullary thyroid carcinoma, and parathyroid hyperplasia) the high level of circulating amines from the pheochromocytoma augments endocrine dysfunction. Forty surgically proven cases of pheochromocytoma were analyzed for age, sex, race, and urinary amine metabolites. The development of subsequent endocrine dysfunction was compared to a control group of patients with diabetes mellitus. A significantly greater proportion of patients with pheochromocytoma developed further endocrine dysfunction which appears to be unrelated to age, sex, and possibly genetics. Problems inherent in a retrospective cohort study and small sample size are discussed.

The function of biogenic amines (Fig. 1) in maintaining balance among endocrine physiologic processes is elusive. In studying biogenic amines, it is important to analyze their effect both centrally and peripherally (1). It has long been appreciated that these compounds can mediate the release of brain peptide hormones and pituitary hormones (2). This study will focus on the less well documented alterations induced by amines on peptide hormone release from the peripheral endocrine tissues.

The importance of amines in endocrine physiology and pathophysiology was highlighted in the pioneering work of Pearse in 1966 (3, 4). He described the presence of specialized cells throughout the body, some in endocrine and others in nonendocrine tissues. These cells share a number of cytochemical and ultrastructural characteristics. First, they all contain secretory granules capable of releasing small peptides. Second, they all have the capacity to take up amines, or their precursors, and decarboxylate them within the cell. He named this scattered system of cells, all of which have a common metabolic, synthetic, storage, and secretion mechanism, the APUD system (for Amine, Precursor, Uptake, and Decarboxylation). Pearse further speculated that these cells all have a common embryologic heritage in the neural crest. This has been vigorously challenged (5–9) and it now appears that the unifying principle behind the APUD concept is not their common embryologic origin, but rather their biochemical similarities (10).

There is experimental and clinical evidence that biogenic amines have a peripheral action. Studies to date have shown that glucose induced insulin release is inhibited by exogenous epinephrine and norepinephrine (11, 12). Examinations of pancreatic islet cells have shown that glucagon release was stimulated by norepinephrine (13), and thereby implicate a convenient agonist-antagonist role for the catecholamines in the maintenance of blood sugar because of their reciprocal effects on insulin and glucagon. Additionally, the amine precursor L-Dopa was shown to stimulate glucagon release in man (14). Baylin has recently discovered that L-Dopa in vivo has a suppressive effect on the basal and stimulated se-

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This paper was written when the author was a third-year student at the Mount Sinai School of Medicine.

1a) *Catecholamines:*

$$\text{Phenylalanine} \xrightarrow{\text{Phenylalinine Hydroxylase}} \text{Tyrosine} \xrightarrow{\text{Tyrosine Hydroxylase}} \textit{DOPA}$$

$$\xrightarrow{\text{Decarboxylase}} \text{Dopamine} \xrightarrow{\text{Hydroxylase}} \textit{Norepinephrine}$$

$$\xrightarrow{\text{Methyltransferase}} \textit{Epinephrine}$$

2a) *Indoleamines:*

$$\text{Tryptophan} \xrightarrow{\text{Tryptophan Hydroxylase}} \text{5-Hydroxytryptophan} \xrightarrow{\text{Decarboxylase}} \textit{Serotonin}$$

FIG. 1. Catecholamines and their biosynthetic pathways.

cretion of calcitonin from medullary thyroid carcinoma (1). Furthermore, in patients with medullary thyroid carcinoma, adrenergic blockade augments the calcium stimulated calcitonin release (15). Of the indoleamines, serotonin has been implicated in the cyclic release of ACTH from the pituitary, with both entities having roughly parallel diurnal patterns of release (16). Serotonin was also found to be actively sequestered by thyroid C cells (that is, the cells from which medullary thyroid carcinoma develops) (17). Finally, it has been observed that the resistance of tissues to tumor growth under conditions of adrenergic excitation (stress) is lowered (18).

The above evidence clearly shows that amines influence peripheral endocrine tissue. One way in which they may occur is via the interaction of amines and the APUD system of cells (1). Support for this idea comes from studies of ectopic hormone production by tumors, and their subsequent production of inappropriate endocrine syndromes. Baylin and Mendelsohn report:

> . . . most tumors associated with well defined syndromes due to excess secretion of small poly peptide hormones and/or biogenic amines (. . . Cushings, inappropriate ADH, excess production of pancreatic islet hormones, pheochromocytoma, carcinoid, watery diarrhea syndrome) possess APUD properties. This fact can be particularly well appreciated when one examines the tumor types associated with excess production of biologically active ACTH. In almost every instance APUD properties are a property of these neoplasms (10).

However, non-APUD tumors can contain significant quantities of such peptides (19). Nevertheless the highest hormone levels are present in the APUD tumors (20, 21). For example, immunoreactive ACTH has been found in lung tumors of all histologic types (20–22), APUD and non-APUD. However, the inappropriate endocrine syndromes occur only when associated with the APUD tumors (10). Therefore, what seems unique about the APUD tumors is that they elaborate the biologically active as opposed to only the immunoreactive peptides. It seems apparent that the absence of inappropriate endocrine syndromes in the non-APUD tumors is not due to their inability to produce immunoreactive hormone, but instead relates to their inability to cleave and package the hormone involved (10). In support of this idea, several immunoreactive forms of peptides, such as ACTH and calcitonin, when found in non-APUD tumors are the biologically inactive prohormone (10, 20, 23). This has led Baylin to theorize that the characteristic secretory granules of the APUD cells contain the biochemical pathways for the posttranslational steps necessary for the production of intact biologically active hormone. Therefore, the posttranslational modification of prohormones into the active form of the hormone appears to be a key function of biogenic amines on peripheral endocrine tissue.

Pheochromocytoma is the adrenal medullary carcinoma which is associated with increased production and high circulating levels of epinephrine and norepinephrine. It is interesting that pheochromocytoma is often associated with a host of other endocrine abnormalities. In 1961, Sipple reported that thyroid carcinoma was fourteen times more common in pheochromocytoma than in the general population (24). Shortly thereafter, Williams observed that the thyroid carcinoma was of the medullary type (25). In 1963, Steinner further suggested that the combination of medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism be called multiple endocrine neoplasia type 2 (MEN-2) or Sipples syndrome (26). However, today it is known that the syndrome has many clinical variations (such as MEN-2b which further includes alimentary tract ganglioneuromatosis, and marfinoid skeletal abnormalities) (27). Pheochromocytoma has been further associated with Cushing's syndrome (28), papillary carcinoma of the thyroid (30), acute lymphoblastic leukemia (31), parathyroid cysts (32), ACTH producing pheochromocytoma (33), diffuse toxic goiter (34), and diabetes mellitus (35).

In light of the previous discussion, an interesting speculation is that the heightened exposure to the amines produced by the tumor may be playing a role in the development of further endocrine abnormalities. Presumably, a heightened amine load would induce a hyperplasia in the tissue (due to an increased post-translational modification of the prohormone) with an increased risk of mitotic error and hence, an increase in carcinoma (Fig. 2a). An alternative explanation is that amines which stimulate Beta receptors (norepinephrine) cause a marked increase in intracellular cAMP. A direct correlation between cAMP levels and the stimulation of growth of normal tissue in vivo has been established (36). Similarly, a decrease in hormone production (for example, diabetes mellitus) may be linked to adrenergic stimulation (with a concomitant decrease in cAMP) of the pancreatic B-cell (Fig. 2b). The action of amines is most likely multifactorial.

Studies aimed at elucidating the role of pheochromocytoma and its relationship with the other endocrine conditions of MEN-2 are characterized by marked disagreement. In 1973, it was reported that the hyperthyroidism was only transient and disappeared after removal of the pheochromocytoma (32–38). The conclusion of these studies was that the increased catecholamines probably stimulated the parathyroids to produce excessive parathyroid hormone. However, Miller's group at the Mayo Clinic challenged this work with its epidemiologic studies on parathyroid function in patients with pheochromocytoma (39). They conclude that parahormone excess occurred infrequently with pheochromocytoma and, when it did, it was not caused by catecholamine excess but rather by genetic causes. Both of these arguments were refuted by the work of Skrabanek who reported that the hypercalcuria and hypercalcemia in pheochromocytoma was not due to hyperparathyroidism but to the direct effect of catecholamines on bone and kidney function (40).

One aspect of the syndrome is the role of inheritance. Twenty to twenty-five percent of the total case load of pheochromocytoma is thought to be of genetic origin as determined by familial studies (41). However, no chromosomal abnormality has been found in this syndrome (42). Genetic analysis of the MEN syndromes (43) have concluded that the associated neoplasms fit into a two-mutation model. By this mechanism, the first mutation occurs in germinal cells and is inherited through an autosomal dominant mechanism. The second mutational event occurs in the somatic cells in the post-zygotic period. The key here is the second mutational event. It is entirely possible that an increase in circulating catecholamines could increase the growth rate (by the above mechanisms) and thereby predispose the tissue to the second mitotic event. In support of this argument are the observations that amines and their precursors have been taken up into many of the tissues involved with the MEN syndromes (1, 33).

Study Proposal

This study attempts to answer the following questions.

1) What is the incidence and nature of disease occurring in patients after detection of a pheochromocytoma?

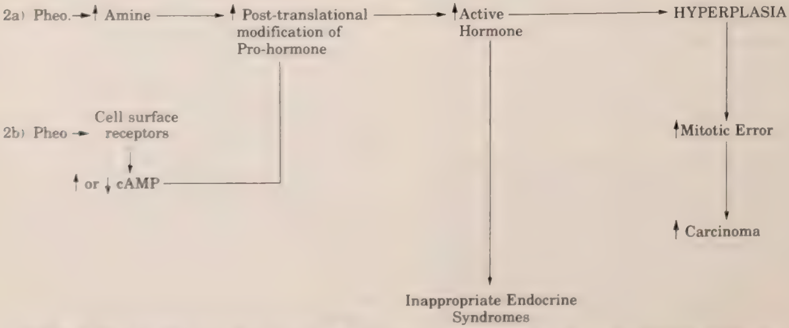

2a) Pheo. → ↑ Amine
↑ Post-translational modification of Pro-hormone
↑ Active Hormone
HYPERPLASIA
↑ Mitotic Error
↑ Carcinoma
2b) Pheo → Cell surface receptors
↑ or ↓ cAMP
Inappropriate Endocrine Syndromes

FIG. 2a,b Two possible ways that amines affect peripheral endocrine tissue and how they may interrelate.

2) Is there any significant age, sex, or race difference among the pheochromocytoma patients in regard to the development of further endocrine dysfunction?
3) Is there any difference between the pheochromocytoma patients with high or low levels of circulating amines, and the development of endocrine dysfunction?
4) Is there significant remission of disease which was present before the pheochromocytoma was removed?

Materials and Methods

Forty records of cases of surgical removal of a pheochromocytoma between 1964 and 1980 were obtained from the office of Dr. Pertsemlidis of The Mount Sinai Hospital. Follow-up information was obtained from the records of Dr. Pertsemlidis or through contact with the patient's primary care physician. In this way, follow-ups on all patients were obtained. Eighty percent had follow-ups until 1980. Name, age, sex, pre- and post-operative urinary amine metabolite levels, approximate date of onset of symptoms, date of surgery, and the subsequent development of medical and surgical conditions after removal of the pheochromocytoma were obtained for each patient. The postoperative return of the urinary amine metabolites to normal was assumed to represent complete removal of the tumor. In all cases, pheochromocytoma was confirmed by tissue diagnosis in The Mount Sinai Medical Center, Department of Pathology.

The control group consisted of forty patients with diabetes mellitus randomly selected from Mount Sinai's diabetes clinic. Name, age, sex, race, date of onset, and subsequent medical and surgical conditions were extracted from the charts. Since all the patients were followed in the clinic, 100% of the charts were current to 1980. Therefore, both the experimental and control groups were actively being followed endocrinologically, and differed primarily with respect to amine exposure and surgery. The groups were not matched for age, sex, or race. However Table Ia–c compares the experimental and control groups with respect to these parameters. Table Ia shows that the control group at the onset of diabetes mellitus is older than the pheochromocytoma patients when they had surgical removal of the tumor. This age difference is not a major confounding factor, because we would normally expect to see more medical and surgical dysfunction in an older group rather than in a young group. Therefore, if there is significantly more dysfunction in the young pheochromocytoma group than in the older control group, this would indicate that something additional is happening in the pheochromocytoma group. Table Ib shows that the sex distribution between the groups is very similar. Table Ic shows that the pheochromocytoma group has a much higher percentage of whites than the control group. This data is skewed because the pheochromocytoma records were obtained from a private surgeon's office and the control records were obtained from the medical clinics. Therefore, it is possible that the influence of race may be a potential confounding factor.

TABLE I

Comparability of the experimental and control group, with respect to age, sex, and race

		PHEO.		CONTROL	
		#	%	#	%
a) *AGE:*	≤19	12	30%	4	10%
	>19 ≤ 40	17	42.5%	14	35%
	>40	11	27.5%	22	55%
b) *SEX:*	♂	19	47.5%	18	45%
	♀	21	52.5%	22	55%
c) *RACE:*	White	25	62.5%	12	30%
	Non-White	15	37.5%	28	70%

Results

In the study proposal section, the first question asks about the incidence and nature of disease occurring in patients after detection of a pheochromocytoma. To assess the nature of disease in these people, all the health problems after detection of the pheochromocytoma were grouped in categories ranging from very general conditions to specific diseases. This approach allowed a factoring out of individual diseases so that specific situations could be studied statistically. The groupings, which were applied to both experimental and control groups, are:

1. development of all further medical and surgical conditions including recurrences.
2. development of all further endocrine conditions, not including recurrent pheochromocytomas. Diabetes mellitus was also not included in the pheochromocytoma group due to high incidence in the general population. Table II outlines the specific conditions.
3. all further medullary thyroid carcinoma and/or parathyroid hyperplasia.
4. all further medullary thyroid hyperplasia
5. all further parathyroid hyperplasia
6. all further breast conditions.

In each category the number of individuals having or not having the condition was noted for both groups. A chi-square test of statistical significance was performed. When the number of cases

TABLE II

Results of study proposal #1: the incidence and nature of disease after detection of a pheochromocytoma

	P value	Yates correc.	Significance	Level
1) All further medical and surgical conditions	2.04	—	no	—
2) All endocrine conditions (no recurrences or diabetes mellitus in pheo. group*)	11.6	—	yes	p = .001
3) Medullary thyroid carcinoma & parathyroid hyperplasia	4.1	yes	yes	p = .05; with Yates, signif. only w/p = .1
4) Medullary thyroid carcinoma *ONLY*.	4.21	yes	yes	p = .05 also at p = .05 w/Yates
5) Parathyroid hyperplasia *ONLY*.	3.12	no	no	p = .05; signif. at p = .1
6) Breast conditions *ONLY*.	1.92	no	no	p = .05

* Includes medullary thyroid ca., parathyroid hyperplasia, thyroid goiter, breast pathology, uterine and testicular pathology.

in an individual test cell was less than five, a Yates correction test for continuity was performed. Table II shows that:

1. There is no significant difference between the experimental groups and the control groups in the development of further medical and surgical conditions.
2. There is a highly significant (p = .001) difference between the groups in the development of further endocrine conditions.
3. There is a significant difference (p = .05) between the groups in the development of medullary thyroid carcinoma and/or parathyroid hyperplasia. However, when Yates correction factor is applied, this is significant only to p = 0.1.
4. There is a significant difference between groups (p = .05) in the development of medullary thyroid carcinoma.
5. There is no difference between groups in the development of parathyroid hyperplasia at p = .05, but there is at p = .1.
6. There is no difference in the development of breast disease between the groups.

Question two of the study proposal is concerned with whether or not there is any significant age, sex or race difference in the development of further conditions between the groups. Only the development of future endocrine conditions was examined because of the large number of cases and its statistical significance in the findings above. The age distribution was arbitrarily broken into three groups: ≤19, >19, ≤40, and >40. From this framework three questions were asked: do young, middle aged, or older pheochromocytoma patients differ respectively from young, middle aged, and older controls in the development of further endocrine dysfunction? Again, the number of individuals having or not having the condition was noted for both groups and a chi square test of statistical significance was performed, and reenforced with a Yates correction for continuity whenever a test cell contained less than five individuals. Table III shows that, statistically, mid-aged and older pheochromocytoma patients develop more endocrine dysfunction than controls. No statistical significance is reported for the young group. The next question asks if male and female pheochromocytoma patients differ respectively from male and female controls in regard to the development of future endocrine dysfunction. Table III shows male and female pheochromocytoma patients both develop statistically more endocrine dysfunction (p = .05) than the respective male and female control groups.

Nothing can definitely be said about racial differences between the pheochromocytoma group and the control group. Therefore, no test of statistical significance was performed for this parameter.

Whether or not the pheochromocytoma patients with very high amine levels were at a greater risk of developing further endocrine dysfunction than other pheochromocytoma patients with lower amine levels is considered in study proposal number three. To answer this question, the pheochromocytoma group was divided into those who did develop further endocrine dysfunction (24 patients) and those who did not (16 patients). With both of these groups, the mean vanillmanilic acid and total metenephrines were calculated (Fig. 3). A *t*-test of statistical significance was applied to these means and the results are in Table IV. There was no significant difference between the average amine levels of those pheochromocytoma patients who progressed to further endocrine dysfunction, and those pheochromocytoma patients who did not, even when the

TABLE III

Results of study proposal #2: Chi-square tests for age and sex

4a)	*QUESTION:*	Do young pheos. differ from young controls in the development of further endocrine dysfunction?
	ANSWER:	NO—P = .76/Level: p = .05
	QUESTION:	Do mid-aged pheos. differ from mid-aged controls in the development of further endocrine dysfunction?
	ANSWER:	YES—P = 5.8/Level: p = .05
	QUESTION:	Do older pheos. differ from older controls in the development of further endocrine dysfunction?
	ANSWER:	YES—P = 5.3/Level: p = .05
4b)	*QUESTION:*	Do male pheos. differ from male controls in the development of further endocrine dysfunction?
	ANSWER:	YES—P = 6.68/Level: p = .05
	QUESTION:	Do female pheos. differ from female controls in development of further endocrine dysfunction?
	ANSWER:	YES—P = 5.22/Level: p = .05

high and low values were dropped from the calculations.

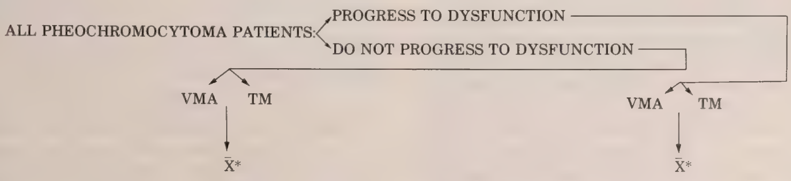
The fourth question deals with the remission of disease after the pheochromocytoma (the amine source) was removed. Up to this point only the occurrence of new conditions has been addressed. Did any disease present before the removal of the pheochromocytoma disappear after it was removed? After analyzing the data, the only disease seen to be alleviated after removal of the tumor was diabetes mellitus. The two reported cases were not statistically significant. However, no diabetes mellitus was observed to have disappeared in the control group.

Discussion

Evidence has been presented that there is a significant difference between pheochromocytoma patients and a control group in the development of further endocrine dysfunction. This finding supports the notion that high levels of circulating amines may be involved in the development of endocrine pathology. Even though the two groups vary primarily in respect to amine exposure, other potential outstanding factors must be considered in order to clearly assess the results.

First, it must be remembered that pheochromocytoma is often a part of a genetic syndrome (43). The degree to which genetics have influenced the results of this study are largely unknown. However, if the presumed 20% to 25% of genetic cases are deleted from the group of pheochromocytoma patients who develop further endocrine conditions, and the chi square statistic is repeated on this group, there are still statistically more pheochromocytoma patients progressing to further endocrine conditions than controls (p = .05). This finding implies that in addition to the known genetic influences, there is possibly another factor operating in the pheochromocytoma group to produce this difference.

This observed difference may just be an artifact of small sample size. With a small sample size, there is a chance of attributing significance where there is none, and also of losing significance which would emerge with a greater number of cases. This is clearly illustrated by the lack of significance of remission of diabetes mellitus after removal of the pheochromocytoma. This phenomenon has been suggested (11) and should


ALL PHEOCHROMOCYTOMA PATIENTS:
PROGRESS TO DYSFUNCTION
DO NOT PROGRESS TO DYSFUNCTION
VMA
TM
$\bar{X}$*
VMA
TM
$\bar{X}$*

* Therefore, the mean amine level is obtained for each group and a t-test is performed on these means. To simplify the calculations for this test it was assumed that the sample variability was equivalent for each group.

FIG. 3. Way in which t-test was set up for study proposal #3.

TABLE IV

Results of t-test for significance for study question #3

QUESTION:	Is there a difference between the mean catecholamine levels amongst those "pheo" patients who progress to other endocrine dysfunction and those "pheo" patients who do not?
ANSWER:	NO. $t = 0.045$

be considered carefully, especially in light of no remissions of diabetes mellitus in the control group (all of whose members had diabetes). Sample size is also important in the observed lack of significance in the development of parathyroid hyperplasia. If the number of pheochromocytoma patients with this condition was increased by one, then it would become significant at $p = .05$.

It was shown that middle aged and older pheochromocytoma patients develop more endocrine dysfunction than the respective controls. Additionally, no difference was shown for children. This finding for children may be related to two factors. First, it may simply reflect more dysfunction in older groups, which is normally expected. Secondly, it may be that the younger individuals have not had enough time to develop the related endocrine problems. Nevertheless, there is more endocrine dysfunction in the older pheochromocytoma group than in the older control group. This finding indicates that something in addition to age is occurring. Similarly, sex was not seen to be a confounding factor since both sexes developed more endocrine dysfunction than the respective sexes in the control group. This again indicates that in a pheochromocytoma group, something in addition to a sex difference is causing the development of further endocrine health problems.

If, as the evidence indicates, pheochromocytoma is associated with the production of further endocrine dysfunction, and factors such as age or sex are not involved in the development of this dysfunction, what then is producing the difference? Genetics are one possibility but probably not in all cases. In view of the literature survey, biogenic amines are likely candidates for the production of this difference. If this is true, then the finding of no difference in average amine levels of the pheochromocytoma patients who progressed to further endocrine dysfunction, and those who did not, appears to refute this argument. But when dealing with exposures, it is the net exposure that counts. Net exposure is the result of the level of exposure and the duration of exposure. The amine levels that were used in this study in no way reflected the duration of exposure and therefore did not measure net exposure. As a result, the finding of no difference between the mean level and the development of future dysfunction is essentially meaningless, and the possibility of a significant difference remains. This problem of not being able to control various aspects of the study from the beginning is an inherent problem of retrospective cohort studies.

Summary

This study sought to assess the current concept of amines playing a role in the development of endocrine dysfunction and carcinoma. The aim of the study was not to elucidate the mechanisms of action of biogenic amines, but to test the hypothesis that they affect normal physiology by looking for any difference in the health profile of a population exposed to high circulating levels of biogenic amines and comparing it to a population that was followed endocrinologically, but which was not exposed to high levels of amines. The results indicate that a statistically greater proportion of pheochromocytoma patients progress to further endocrine pathology. Age and sex were not found to be significant in this trend. The influence of race was not examined in this study and may represent a potential confounding factor. Genetic factors were reviewed and were shown to be important in the development of endocrine pathology but are not felt to be able to explain all further development of endocrine dysfunction and the associated wide variability of dysfunction in the pheochromocytoma patient. The small sample size and the problems associated with a retrospective cohort study have been recognized as a potential confounding factors. Nevertheless, in light of the large statistical difference between groups, the persistence of this difference for most of the specific conditions examined, and the further persistence of this difference after a genetic subgroup was removed, it is suggested that amines may indeed have a role in the development of endocrine pathology.

Acknowledgments

The author would like to thank Dr. Shatzkin from the Community Medicine Department and Dr. Pertsemlidis from the Department of Surgery for their valuable time, assistance and encouragement.

Data for this study was collected from the office of Dr. Pertsemlidis, and the clinics of The Mount Sinai Medical Center.

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Submitted for publication March 1981.

The Mount Sinai Journal of Medicine
Vol. 50, No. 3, May–June, 1983
Printed in U.S.A.

Student's Corner

Barry Berson, B.A., Editor

Kaposi's Sarcoma of the Rectum: A Case Report

James Bianco, B.S., and Loretta Pratt-Bianco, M.D.

Abstract

An unusual case of Kaposi's sarcoma is reported. The patient was admitted to the hospital because of nine months of rectal pain and bleeding. The incidental finding of a submucosal rectal nodule at the time of anal fissure repair revealed, on biopsy, rectal mucosa infiltrated with Kaposi's sarcoma.

Multiple idiopathic pigmented hemangiosarcoma was described by Moricz Kaposi in 1872 as a fatal disease with the manifestation of multiple vascular nodules (1, 2). He noted that these lesions occurred most commonly on the skin of the extremities, but was aware that they could involve internal organs. Kaposi believed that the disease was a sarcoma of multifocal origin the treatment of which was, at best, palliative.

The disease generally presents as red-purple nodules, plaques, and macules. Initial lesions are usually located peripherally on the extremities, but may appear anywhere on the skin, mucous membranes, or internal organs. Although the most common presentation of Kaposi's sarcoma is the cutaneous form, associated visceral involvement is not unusual (3–8). It was originally reported in about 10% of the cases (9); however, in more recent necropsy studies the incidence is higher (8). The gastrointestinal tract is the most common site of visceral involvement, particularly the small bowel; the liver, stomach, and colon are less commonly involved (5, 10).

Cases of primary gastrointestinal involvement without skin involvement have been documented but are rare (11, 12). It is not widely appreciated that symptomatic gastrointestinal Kaposi's sarcoma may overshadow minor skin lesions and may precede or occur in the complete absence of cutaneous disease. This report concerns a case in which Kaposi's sarcoma of the bowel preceded the cutaneous lesions.

Case Report

The patient is a 26-year-old white homosexual male who was initially admitted to The Mount Sinai Hospital in December 1981 because of prolonged rectal pain and bleeding. The patient's symptoms were refractory to conservative management and surgery was recommended. On rectal examination, he was found to have severe pain and evidence of a posterior anal fissure. The patient underwent a sphincterotomy and excision of posterior anal fissure. An incidental finding at the time of surgery was a mass in the rectum 1 × 1 cm anteriorly placed, and 2 cm cephalad from the anal verge. The biopsied specimen revealed Kaposi's sarcoma.

The patient was discharged and readmitted at a later date (February 1982) for wide and deep excision of rectal tumor. His medical history revealed multiple episodes of hepatitis, amebiasis, rectal and genital herpes, cytomegalovirus infection, giardiasis, and infectious mononucleosis. Pertinent social history includes a 26-year-old homosexual male with over 50 sexual contacts a year who frequently uses amyl and butyl nitrates and amphetamines and occasionally uses marijuana.

Physical examination on admission revealed a thin white male in no acute distress with stable vital signs. Examination of the neck revealed a firm, nontender, 2 × 2 cm right supraclavicular node. Perianal erythema and excoriation was noted on rectal examination. No obvious mass was palpable; the stool guaiac was negative. The rest of the physical exam was unremarkable. Laboratory tests on admission revealed severe anemia (hematocrit 25, hemoglobin 8.7) and leukopenia (white-cell count 3,400). Urinalysis,

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This article was written when the first author was a third-year student at the Mount Sinai School of Medicine and the second author was an intern at St. Vincent's Hospital, New York City.

electrocardiogram, chest x-ray, and SMA 6 were all within normal limits.

After a limited bowel preparation, the patient was taken to the operating room, where he had a wide and deep excision of his rectal lesion. The frozen section showed rectal tissue with spindle cells and vascular proliferation suggestive of Kaposi's sarcoma. The patient's postoperative course was essentially uneventful and the patient was discharged in satisfactory condition to be followed by his private physician. The final pathology report showed rectal mucosa extensively infiltrated by Kaposi's sarcoma.

Discussion

Kaposi's sarcoma is now recognized to be a systemic disease, although skin lesions are the initial presenting complaints in the majority of patients. Gastrointestinal symptoms when present are variable and have included abdominal pain, melena, and obstruction (13, 14). Less frequently, intussusception, hematemesis, perforation, and peritonitis may occur (15, 16). In view of the pathologic findings in gastrointestinal Kaposi's sarcoma (5), it is difficult to understand why more patients are not symptomatic. The disease begins in the submucosa and produces intraluminal nodular growths. The overlying mucosa is often attenuated and infiltrated and occasionally ulcerated. Radiographic examination usually demonstrates multiple small nodular defects, localized mucosal thickening, and irregularities of the contours of the segment involved (3, 4). The roentgen differential diagnosis includes entities which produce a pattern of diffuse multiple intestinal nodules. Besides lymphoma, metastatic neoplasm (especially melanoma), amyloidosis, and submucosal hemorrhage must be included in the differential diagnosis (17–19).

Soft tissue sarcomas are uncommon neoplasms representing 0.3%–0.4% of all malignancies. Kaposi's sarcoma occurs in about 1% of this group (20). The cause of Kaposi's sarcoma remains unknown. The rarity of more than one case of this disease in a family negates the possibility of simple Mendelian dominant-recessive inheritance, unless one assumes that an extreme amount of incomplete penetrance is involved. The increased incidence of Kaposi's sarcoma in renal transplant recipients suggests that immunosuppression may be important in the development of the disease. Further support comes from the association between lymphomas and Kaposi's sarcoma (24, 25), generalized lymphomas are frequently associated with depression of the cellular immune system.

Giraldo et al (21–23) have indicated a possible infectious cause involving cytomegalovirus (CMV) in the pathogenesis of Kaposi's sarcoma. These authors demonstrated herpes-type viral particles in tissue culture lines of patients with Kaposi's sarcoma (21). They further demonstrated a close serologic association between CMV and Kaposi's sarcoma (23). Serologic evidence of past CMV infection was recently reported to be more than two times as frequent among homosexual men as among unselected heterosexual male volunteer blood donors (26). Ninety-four percent of homosexual men in that study had had past CMV infection, and none of the heterosexual controls had evidence of CMV infection. It seems, then, that a significant percentage of the homosexual population has asymptomatic CMV infection with active virus shedding (26). It is interesting to speculate on the etiologic role of CMV infection in the homosexually related immunodeficiency syndrome (GRID). CMV has been shown to diminish the response of monocytes to certain mitogens and, as such, is immunosuppressive. An induced population of suppressor cells is thought to be the basis of this immunosuppression (27).

It has recently been suggested that chronic multiorganismal infection, which is frequent in the homosexual community, could lead to immunodeficiency (28, 29). With the endemic distribution of intestinal infections in Africa, and the fulminating form of Kaposi's sarcoma seen there, one can speculate whether the widespread parasitic infection in homosexuals in the Western world prompted a similar form of Kaposi's sarcoma to develop. Kaposi's sarcoma as it is classically reported in the United States is often described as indolent in nature with a pattern of slow, progressive growth. It is more common in Jewish and Italian groups and typically involves the dermis of the lower extremities. In contrast to the indolent American form of Kaposi's sarcoma, there exists a form endemic to parts of central and southern Africa, where the disease is relatively common. This African form is more fulminant and found in both adults and children. It occurs as a systemic disease with generalized lymphadenopathy, anemia, and hepatosplenomegaly and usually without skin manifestations. This form is associated with a poor prognosis, most victims dying within three years of presentation (10).

The similarity between the type of Kaposi's sarcoma currently identified in the homosexual community and that commonly seen in Africa is of interest. It should be stressed that prior to a recent outbreak (July 1982, CDC report of 26 cases), the fulminating form of Kaposi's sarcoma was extremely rare in this country. Only in groups of immunosuppressed patients has the disease been observed with increasing frequency (31).

The treatment of Kaposi's sarcoma has generally been limited to radiation and chemotherapy. Surgery has been limited to biopsy or excision of solitary nodules (32, 33). Clearly, more detailed studies are needed to further elucidate the etiologic and pathogenetic factors and most effective treatment regimens for Kaposi's sarcoma.

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Submitted for publication June 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Bernard H. Eliasberg, M.D.

Twentieth Bernard H. Eliasberg Memorial Symposium

Intravenous Anesthesia—Current Status

Sponsored by the Department of Anesthesiology and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY)

Held December 4, 1982 at The Mount Sinai Medical Center

Supported in part by an educational grant from Janssen Pharmaceutica

Introduction

Dr. Bernard H. Eliasberg had a happy association with The Mount Sinai Hospital for some 56 years. Having joined the house staff in 1906, he was appointed anesthetist to the hospital in 1910. He and Charles Elsberg first described insufflation anesthesia as a means of achieving oxygenation during thoracic surgery, and while in no sense could this be considered comparable to high-pressure jet ventilation as we know it today, there are certain similarities in the two methods, namely the production of a very still lung and the absence of serious adverse effects on the cardiac output.

Dr. Eliasberg was promoted to chief of the Department in 1943, a position he held for some seven years. Relinquishing that administrative task in 1950, he remained on the active consulting staff until he died in 1962.

Dr. Eliasberg was one of the founders of The New York Society of Anesthetists, which eventually begot the American Society of Anesthesiologists. He was also an early diplomate of the

American Board of Anesthesiology. His opinion, based on wide experience and learning, was constantly sought by his colleagues, and he was one of a vanishing breed of gracious gentlemen of the "old school." He could successfully pour oil on almost any troubled water. In addition, he was endowed with a deep sense of humor and great facility as an after-dinner speaker. It is therefore with awe and reverence that we honor his name today.

Through the generosity of the Eliasberg family we have been able to perpetuate his memory in a professional way. Initially this took the form of a social evening to which one of the leaders of science or anesthesiology—Pauling and Kety among them—was invited as a special guest. As continuing medical education activities developed, it became appropriate to expand the format into a half or a whole day symposium on a suitable topic. To my mind this is a much more meaningful and effective way of paying homage, an attitude which I think Dr. Eliasberg would himself endorse in the light of his great love of teaching.

Last year the symposium was entitled "Morphine after 2000 Years," and I introduced the proceedings by showing a short film (in itself a scrap of cinematic history) made by Sir Robert McIntosh at Oxford prior to the outbreak of World War II. The first half of the film concerns an attempt to produce anesthesia for herniorrhaphy by the administration of alcohol intravenously. The second part of the film, which would probably raise the hackles of any self-respecting Research Advisory Committee today, concerns the use of morphine as the sole anesthetic during appendectomy. It is to intravenous anesthesia—the subject of our symposium—that I now direct your attention.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Barbiturates

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It is now nearly fifty years since the successful introduction of intravenous barbiturate anesthesia with sodium thiopental, and over twenty years since the shorter acting methohexital was introduced (1, 2). Few intravenous drugs have been studied more extensively or subjected to such wide clinical use. While other anesthetic agents such as ether, methoxyflurane, cyclopropane, trichloroethylene, and propanadid have largely fallen into disuse, the ultrashortacting barbiturates have kept their supremacy in anesthesia.

Alongside the recent interest in the development of new intravenous anesthetics, there have been new discoveries about the barbiturates. This paper addresses some of the newer findings, grouped under the headings pharmacodynamics, central nervous system effects and mode of action, circulatory actions, use in obstetrics, and adverse effects.

Pharmacodynamics

Unconsciousness is produced within one arm-brain circulation time or ten to fifteen seconds following a bolus injection of a sleep dose of thiopental. This is due primarily to the high lipid solubility of the un-ionized 61% of the drug, even though a lot is protein-bound (65%-86%) mainly to albumin (2, 3). Penetration of the brain is rapid. It can be said that the blood-brain barrier does not exist for this drug (2). Within thirty seconds, plasma and brain concentrations of thiopental are in equilibrium and within sixty seconds the other tissues of the vessel-rich group including heart, liver, kidney, and gastrointestinal tract, have also achieved equilibrium (2, 3).

Recovery of consciousness is in five to ten minutes. This is due to the rapid rate of exit of the lipid-soluble drug following the fall in plasma concentration which accompanies redistribution to lean body tissues, especially muscle (4). By five minutes the brain concentration has halved (5). Entry into muscle mass is rapid, equilibration being achieved with plasma concentration by fifteen minutes. By thirty minutes, 80% of the sleep dose is in muscle tissue (2, 4). If redistribution should be delayed by reduced muscle-blood flow, as in shock, the sleep dose can be lethal. A mortality of 1:80 has been reported in early series (4). Although highly fat soluble, only 10% has been redistributed to fat after thirty minutes. This is due to the poor fat blood flow, but over the next two hours, fat is the major site of uptake because of the high fat:blood solubility coefficient, 11:1 (2).

In 1960 Price (5) described a mathematical analysis of the kinetics of thiopental distribution and proved his conclusions by direct measurement of drug concentration in tissues. This showed lean body tissues, especially muscle, as the major site of redistribution and assumed a slow rate of metabolism at 10% to 15% per hour. Mark et al (6) in 1965 showed that the liver could remove up to 50% of thiopental from the hepatic blood flow and therefore played a definite role in the short action of the drug. The following year Saidman and Eger (7) presented a physiological model. They proposed that although uptake in muscle is responsible for the early fall in the arterial concentration, metabolism and uptake by fat do play some role in awakening. It is now thought that a single sleep dose is metabolized at the rate of up to 24% per hour, with small amounts also being metabolized in kidney and brain (8).

In 1981 Morrel and van Hoorn Hickman (9), after further work with a liver preparation perfused with thiopental, made a new suggestion. They proposed that since the liver is capable of metabolizing far more thiopental than is normally presented to it, the rate of elimination from the whole body is restrained predominantly by release from deep peripheral compartments, especially fat. Methohexital being less fat-soluble is not so trapped, and is therefore more readily me-

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tabolized. The claims of rapid awakening and milder hangover effect for this drug are based on this pharmacodynamic effect.

Following Price's and Saidman and Eger's models, Stanski (10), in 1980, applied the new concepts of compartment analysis to these two barbiturates. He described distribution and elimination half-lives and showed that thiopental exhibits three-compartment behavior, whereas only two compartments are needed to characterize methohexital. Methohexital has a short elimination half-life of 97 minutes, whereas that for thiopental is four hundred three minutes. The volume of distribution at a steady state for thiopental is approximately twice that of methohexital, because thiopental is more fat-soluble. The clearance of methohexital is approximately four times higher than thiopental because the liver has a greater ability to metabolize methohexital and consequently elimination of it is greater (10–12). However, complete recovery of psychomotor and cerebral functions seems to take the same length of time after the use of either of these barbiturates when given in equianesthetic doses (4).

Recent work on the protein binding of thiopental has produced controversy. Wolf et al (13) showed that larger clinical doses produce less protein binding and hence freely expose more drug to the vital organs. Stanski and Burch (14) were unable to duplicate these results. However, it does seem certain that a large decrease in total plasma protein concentration prolongs the recovery time from barbiturate anesthesia (15). The decreased protein binding in uremia and the hypoalbuminemia of cirrhosis is well established.

Several studies on pharmacokinetics in the elderly have shown that sleep and maintenance doses for persons over sixty years old are some 20% to 40% less than for young patients. The difference is due partly to higher cardiac output in the young; it is also probably the result of the slower release from peripheral compartments in the elderly caused by lower blood flow and slower hepatic metabolism (16, 17).

To the list of drugs which can displace the intravenous barbiturates from serum proteins such as aspirin, phenylbutazone, and sulfisoxazole, probenecid has now been added. Probenecid in doses of .5 gm to 1 gm three hours before anesthesia can prolong sleep by 25% to 100% (18).

Recently, following the use of large doses of thiopental by continuous infusion over long periods in head injury, it was found that the pharmacokinetic behavior changes. First-order kinetics, in which a constant percentage or fraction of the drug is cleared from the body in unit time, changes to zero-order kinetic elimination, in which a constant absolute amount is cleared, with larger doses. The clearance mechanisms become saturated with larger doses. Thus a rapid rise in concentration can result from continued administration (3). In at least one case, this has contributed to a fatal outcome when concentrations rose far in excess of those required to maintain sleep in a head injury patient (19).

In an attempt to avoid inhalational agents and operating room pollution, renewed interest is being shown in continuous infusion anesthesia. For this, methohexital has been used alone or in combination with other anesthetic drugs. However, since prolonged recovery is a problem with larger doses, this technique appears to be satisfactory only for shorter procedures (20, 21).

Central Nervous System Effects and Mode of Action

The mode of action of the barbiturates principally on the cerebral cortex and reticular activating system has been further elucidated. Traditionally they are said to stabilize cerebral cellular membranes and elevate excitatory thresholds. Perhaps they do this via their ability to inhibit oxidative phosphorylation and to interfere with adenosine triphosphate formation (8). It now appears that they are able to inactivate phosphofructokinase, inducing a partial metabolic block in the Embden-Meyerhof pathway. Infusion of fructose—one, six diphosphate into the carotid arteries of dogs anesthetized with thiamylal—lightens the anesthetic depth by 50%. This substrate bypasses the metabolic block and greatly reduces the time required for the animal to regain conciousness and walk (22). Fructose-1, 6 diphosphate may be used in the future to lighten barbiturate coma.

Unlike inhalational forms of anesthesia, naloxone does not appear to antagonize thiopental anesthesia, which suggests an endogenous opiate mechanism is not involved (23).

At the microcellular level it appears that barbiturates, at anesthetic concentrations, act in the cerebral cortex and brain stem to inhibit conduction. They inhibit depolarizaton-induced calcium influx across the presynaptic nerve ending and this may, at least in part, mediate sedation and hypnosis. Interestingly, they do not do this in the midbrain and hypothalamus regions, which are not directly associated with maintaining consciousness (24). Work by Macdonald and Barker

(25) on the neuroinhibitory transmitter gamma aminobutryic acid (GABA) has shown that anesthetic barbiturates augment GABA-mediated inhibition. They do this on both sides of the synapse by activating chloride conductance channels, thus hyperpolarizing the cells and decreasing excitation. The barbiturates do not actually bind with GABA receptors per se, but enhance particularly the postsynaptic inhibitory action of GABA (25, 26). With barbiturate anesthesia there is a transient increase in cortical GABA receptor density. This could explain the phenomenon of acute tolerance, in that a greater number of GABA receptors is present with reduced availability of transmitter (27).

New light has also been thrown on acute tolerance. Originally Brodie (28) discovered that thiopental plasma levels on waking were higher after a large dose of the drug than after a smaller one. Dundee et al confirmed these findings and demonstrated that the higher the initial doses of thiopental administered, the greater the increments needed to maintain a constant degree of cerebral depression (29). In 1980, Dundee (30) reexamined acute tolerance with new techniques. He confirmed that plasma thiopental concentration is a poor guide to depth of anesthesia and that concentrations at recovery were higher if higher initial doses had been given. This lack of correlation between plasma thiopental levels and the depth of anesthesia as judged by the electroencephalogram (EEG) is now being reinvestigated with a new technique: spectral edge frequency, which is the highest frequency at which a significant amount of energy is present in the EEG. It appears to provide a simple, rapid and sensitive indicator of anesthetic depth (31). When correlating this with serum thiopental levels, Stanski and coworkers (32) showed the two rose and fell in concert. With repeated infusions over a one-hour period the spectral edge correlated with thiopental levels without any evidence of acute tolerance. This will need future clarification (32, 33).

An extension of the concept of acute tolerance has been proposed by Coté's team in Boston (34). They found that children between ages five and fifteen who had had multiple thiopental anesthetics required much larger sleep doses even up to five years later. A control group who had not had multiple exposure required much less. Acute tolerance may be prolonged in children.

The usefulness of barbiturates in global brain ischemia remains controversial. We are beginning to see light in this situation. In 1982 Todd et al (35) observed the neurologic effect of thiopental therapy following experimental cardiac arrest in cats. They found that in the cats that survived there were no differences in neurological deficits of treated animals compared to controls but there were significantly fewer deaths from neurological dysfunction in the treated group. The incidence of seizure pattern on the EEG was also less. They suggested that suppression of seizure pattern may be achieved with phenytoin, with an improved risk-benefit ratio. In anesthesia the protection of thiopental against cerebral ischemia may be used to advantage. Thiopental reduces cerebral metabolism and oxygen consumption more than cerebral blood flow and therefore increases the cerebral perfusion/metabolism ratio. Some now advocate a sleep dose intraoperatively before a potentially ischemic situation, such as clamping during carotid endarterectomy or hypotension for cerebral aneurysm clipping (36).

Circulatory Actions

One byproduct of barbiturate use in head injury and cerebral ischemia has been the increase in information about the effect of high-dose barbiturate on cardiovascular function. This is producing a reevaluation of thiopental as a cardiac depressant (37). Traditionally, descriptions of the cardiovascular effects of the intravenous drug have first mentioned the dose-related direct myocardial depression with reductions in cardiac output. This reduction varies from 10% to 25% with moderate doses (3–5 mg/kg) to 50% with large doses (9 mg/kg) (2, 3, 8). The increased effects in patients with cardiac disease, hypovolemia, or untreated hypertension is well documented (2, 3, 8).

Two recent studies of the hemodynamic effects of high-dose thiopental have shown that the direct myocardial effects of this drug may be surprisingly small. This is already known for small clinical doses, rapidly injected, but it appears to be true also for larger doses administered slowly. Koht, Mulvehill, and Patt (37) infused 15 mg/kg thiopental over two minutes in normovolemic patients without heart disease and measured vascular pressures with a pulmonary artery catheter. They detected only minor and clinically insignificant changes in heart rate, arterial pressure, cardiac and left ventricular stroke work indices. Todd et al (38) infused 75 mg/kg of drug over one hour in five neurosurgical patients with normal hearts. They simultaneously gave lactated Ringer's solution at sufficient rate to keep the pulmonary capillary wedge pressure at control levels. One to one-and-a-half liters of fluid were needed. It was found that, although some direct myocardial depressant effects occurred, compensatory changes in heart rate were sufficient to maintain cardiac index and blood pressure, and that the main effect was venodilatation, with reduced preload. Provided fluid is infused to counter this, thiopental has minimal effects on vascular pressures and resistances.

Becker and Tonnesen (39) found, when comparing barbiturate to inhalational agents at approximately the same anesthetic depth, that anesthetic barbiturates produced minimal direct cardiac depression. It must be stressed, however, that these data should not be extrapolated to patients with heart disease or hypovolemia.

Use in Obstetrics

For induction of general anesthesia for caesarian section there have been many studies comparing thiopental and methohexital to other agents both for emergency and elective section. Compared to ketamine (1 mg/kg) the barbiturates offer a lower incidence of unpleasant dreams and less maternal hypertension but, unfortunately, lower neurobehavioral scores for the baby (40–43). It is this depressant effect on the baby which has produced a more vigorous search for alternatives in obstetrics. Compared to intravenous barbiturates, the new etomidate, like propanadid a decade ago, appears to produce more lively infants with quicker time to sustained respiration. This is possibly due to inactivation of both drugs by placental cholinesterase (44). A more recent comparison of thiopental 3.5 mg/kg to ketamine 1 mg/kg has shown the overall blood gas-acid base status of both mother and baby were very much the same (45). One study comparing thiopental induction at the relatively high doses of 7 mg/kg to ketamine at 2 mg/kg claimed that neither drug had a negative effect on fetal vitality and that the barbiturate produced better levels of maternal anesthesia and smoother arousal (46). In obstetrics, the barbiturates appear to be holding their ground against the newer induction agents when general anesthesia is needed.

Adverse Effects

While it is accepted that adverse reactions to the intravenous anesthetic barbiturates are rare, an increasing number of hypersensitivity reactions is being reported (47). Until 1971 only 6 cases of anaphylaxis had been reported in the literature; by 1976 the cases had increased to 31, and as of 1982 over 60 reactions to thiopental are recorded. These are mostly of the anaphylactoid type. Fifteen reactions to methohexital have been recorded (47).

Most intravenous anesthetics, with the exception of etomidate and diazepam, produce histamine release and raised plasma histamine concentrations (48). This histamine release may be greatly increased in anaphylactic reactions due to the action of immunoglobulin E (IgE) on mast cells. In the anaphylactoid reactions there is direct release of histamine from mast cells by thiopental or through the activation of complement (49).

The signs of reaction which may occur, rarely on first challenge but more often after multiple exposures, include the immediate development of cyanosis; hypotension; facial, laryngeal or lingual edema; laryngospasm; bronchospasm; massive urticaria. In the last few years the appearance of a bright glowing red or salmon-pink uniform erythema has been particularly reported (50, 51). Allergic reaction to methohexital has been reported two hours after administration (52). Fixed drug eruption has now been added to the list of types of reaction produced by thiopental (47).

In the management of an allergic reaction, Chung (53) has emphasized the importance of ventilatory and cardiovascular support. The drug of first choice is epinephrine. Antihistamines and steroids take a definite second place (53). To date no fatal case of anaphylaxis to thiopental has been reported (53).

Diagnosis of barbiturate-mediated hypersensitivity can be difficult. It is currently advised that blood be drawn into a plain tube and one with the preservative ethylene diamine tetra acetate for IgE and complement determinations. Serial blood samples will often show massive conversion of up to 50% of complement-three via the alternate pathway over a few hours. Unfortunately, this is only indicative of an allergic reaction and not specific for the causative drug (54). Skin testing is inconclusive and intravenous testing may be hazardous (55). The in vitro lymphocyte transformation and leukocyte degranulation tests are still experimental; results depend on the experience of the observer and are not always conclusive. In these tests, animal white cells are exposed to patient's serum, then washed and observed after reexposure to solutions of the barbiturate (53). In theory, a two-week incubation period is optimal for expression of primary sensitization, so perhaps we should be particularly cautious when the second administration of thiopental comes near this two-week interval (51).

Among adverse reactions to intravenous barbiturate anesthetics, hepatotoxicity is not usually considered to be a complication, although doses of thiopental over 750 milligrams can induce liver dysfunction (56). Against this background a case of hepatitis following thiopental was reported from Denmark in 1979 (57). A patient developed unexplained pyrexia up to 41°C and jaundice to bilirubin 4.7 mg/dL. The serum glutamic pyruvate transaminase rose to 1200 and the serum oxaloacetic transaminase rose to 900. This occurred on three occasions following anesthesia for three gynecological procedures over several years. The only feature common to all three anesthetic techniques was thiopental induction. A new anesthetic machine, which had never been contaminated with halothane, was used on the third occasion. After a fourth anesthetic, omitting the intravenous barbiturate, the patient remained apyrexial and the liver enzymes did not rise. This may be a new manifestation of hypersensitivity.

What can be said of the future for new intravenous barbiturate anesthetics? Exhaustive research with variants has produced a host of clinically useless substances. It is now being appreciated that barbiturates are not the structurally nonspecific compounds once thought. If the racemic mixtures, which we use clinically, containing equal parts of optical isomers are separated, then potency varies considerably. It is therefore possible that considerably more potent anesthetic barbiturates may be produced by designing compounds which provide a better three-dimensional fit to the target sites in the brain (58).

Summary

The intravenous barbiturates remain amongst the most widely studied drugs and are the standard for comparison with all new intravenous anesthetics (59). No drug has yet been seriously able to challenge thiopental, which remains the intravenous anesthetic of choice for most anesthesiologists (60). The advantages are readily apparent: rapid smooth onset of action in one arm-brain circulation time, short duration of action with rapid emergence, minimal excitatory effects, good dose response, lack of interaction with muscle relaxants, uncommon adverse reactions, and minimal postoperative vomiting or emergence delirium (61). The disadvantages are also well-known, including respiratory and cardiovascular depression, poor abdominal relaxation, lack of analgesia, and prolonged hangover with slow complete recovery (61).

Although there are many relative contraindications to the use of the barbiturates, the main absolute contraindications are porphyria and known allergy. In most patients the potential for complications can be easily identified by careful history-taking and examination. Although the barbiturates are far from the ideal intravenous anesthetics, most of us have learned to live within their limitations but look forward to the discovery of improved agents for the future.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Benzodiazepines

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Benzodiazepines have broad clinical uses in anesthesiology because they possess a useful combination of important therapeutic properties: they produce sedation, hypnosis, amnesia, and centrally mediated muscle relaxation, in addition to their antianxiety and anticonvulsant effects. As a class the benzodiazepines lack significant side effects outside the central nervous system and have low toxicity. The major factor responsible for their widespread use is the low potential for cardiovascular or respiratory depression when these agents are administered by the oral or intramuscular route.

The discovery of opiate receptors and endogenous opiatelike ligands stimulated the search for and subsequent identification of benzodiazepine receptors, first identified in 1977 (1). The distribution of benzodiazepine receptors in the mammalian brain closely corresponds to that previously determined for gamma-aminobutyric acid (GABA) receptors, and it is now appreciated that the mechanism of action of benzodiazepines is related to the facilitation of GABA effects at postsynaptic receptors in brain and glycine effects within the brain stem and spinal cord (2). Phylogenetic studies suggest that during the course of evolution benzodiazepine receptors appeared in the brain with the development of bony fishes and have subsequently been modified with the evolution of higher vertebrates (3). These receptors are not found in invertebrates. The presence of opiate receptors has also been demonstrated only in vertebrate species.

It now appears likely that binding sites for benzodiazepine and GABA receptors exist in close apposition as a macromolecular complex on the neuronal surface membrane. This complex contains a chloride ion channel, the regulation of which by GABA and its modulators determines neuronal excitability (4). Many substances have been proposed but as yet the existence of an endogenous benzodiazepinelike ligand is unconfirmed (5).

Recent advances in understanding of the neuropharmacology of the benzodiazepines is stimulating research in many areas of great relevance to anesthesiology. It is now appreciated that anesthesia itself may in part be due to an inhibition of GABA metabolism at the synapse, resulting in raised GABA levels and synaptic inhibition. Such effects have recently been demonstrated with halothane, ethrane, and ether (6).

A further area of interest is the use of glycine as the bladder irrigant during transurethral resection of the prostate, a procedure during or after which patients may develop blurred vision and even transient blindness. Such visual disturbances, often attributed to cerebral edema, may be due in part to absorption of large quantities of glycine, a known inhibitory neurotransmitter of the retina (7). These patients often receive spinal anesthesia and diazepam for sedation.

Premedication

A major aim of premedication is to reduce perioperative anxiety. Anxious patients appear to benefit if they have little recall of the day of the operation. Amnesia for perioperative events is therefore frequently desirable, although not all patients wish it.

Drugs which produce amnesia in humans, such as scopolamine and benzodiazepines, do so by selectively depressing those parts of the brain concerned with the registration and consolidation mechanism of memory. In animals, many central nervous system depressants, including general anesthetics, appear to produce retrograde amnesia, but in humans only anterograde amnesia has been demonstrated.

Antirecall and Sedation Effects. Diazepam and lorazepam given orally in doses commonly used for premedication produce a dose-related amnesia (8). However, the sedative and antirecall effects

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of these two agents are not parallel (9). Reports concerning the degree of lack of recall and its significance following oral benzodiazepine administration are inconsistent, with the exception of lorazepam 4 mg; the amnesic effects of this dose are consistently found to be both impressive and of prolonged duration (8, 9). Lorazepam 4 mg orally produces a high degree of amnesia for over four hours after a delay in onset of about 40 minutes (8).

Lorazepam 4 mg is also effective given intramuscularly (10). When given by the intravenous route, lorazepam 2 mg produces good sedation for 3 hours following a latent period of 5 minutes; the antirecall effect, however, is significant in only 50% of cases, has a duration of only 30 minutes, and has a latent period of 30 minutes (11).

After lorazepam 4 mg is given intravenously, good sedation persists for over 6 hours and the antirecall effect occurs within 15 minutes, lasting over 4 hours, with a frequency of 70% to 80% (11). By comparison, intravenous diazepam has a duration of 30 minutes, a peak frequency of 50%, and a latency period of 2 to 3 minutes. Intravenous scopolamine, long the standard agent for comparing amnesic effects, has a duration of action of 90 minutes, a latent period of 60 minutes, and a peak frequency of 90%.

In addition to their sedative, anxiolytic, and amnesic effects, both diazepam and lorazepam are effective in blocking the untoward emergence sequelae of ketamine anesthesia (12).

Anticonvulsant Effects. The benzodiazepines are potent anticonvulsants and antagonize convulsions produced by many pharmacologic agents. This property is of particular importance with respect to local anesthetic agents.

Diazepam is commonly administered in small doses to sedate patients undergoing spinal or epidural anesthesia and field blocks; its anticonvulsant action is an additional beneficial effect. The anticonvulsant action of benzodiazepines on local-anesthetic-induced convulsions is probably due to suppression of local-anesthetic-sensitive limbic seizure generators (13).

In a recent study by de Jong and Bonin, mice were given intraperitoneal doses of lidocaine, bupipacaine, or etidocaine of a magnitude known to produce a 90% convulsant incidence. Pretreatment with intramuscular diazepam, lorazepam, or midazolam markedly reduced the seizure rate (14). Midazolam was the most effective prophylactic agent. All three benzodiazepines also reduced the mortality rate.

In the past decade benzodiazepines given orally have gained great popularity and to a large extent have displaced narcotics, barbiturates, and phenothiazines for preoperative medication. They are well absorbed and effective when administered by the oral route; antacids reduce the rate but not the extent of absorption (15).

Timing. The long duration of action of lorazepam has particular advantages with respect to the timing of premedication; precision timing need not cause concern when delays or cancellations in the operating room schedule occur. A program in which all patients on the day's surgical schedule were premedicated with lorazepam early in the morning would probably prove satisfactory and labor-saving.

However, the prolonged action with consequent hangover effects of the commonly prescribed benzodiazepines, diazepam and lorazepam, reduce the suitability of these drugs for patients undergoing "ambulatory" surgery, where rapidity and completeness of recovery are essential. Temazepam and Tofizopam, recently introduced in Europe, may prove more suitable for patients undergoing surgery without hospital admission. Temazepam, a sedative and anxiolytic agent, does not prolong recovery from anesthesia because of its short half-life and the inactivity of its metabolites (16). Tofizopam may prove of great value, as it produces a marked anxiolytic effect but has no sedative or sleep-inducing actions (17).

Routes of Administration. Intramuscular benzodiazepines cause pain at the injection site which may persist for an hour or more. The incidence of pain with diazepam exceeds 30% in the buttock and 50% in the thigh (18). Flunitrazepam and lorazepam may also cause pain, but much less frequently than does diazepam (19). Diazepam given by the intramuscular route for premedication is not only painful, but often ineffective, and has been almost completely abandoned. Higher plasma levels and better sedation over 90 minutes occur when diazepam is given by mouth (18). The delayed and erratic absorption of diazepam following intramuscular injection is presumed to be due to its low water solubility and is most marked in the obese.

Both flunitrazepam and lorazepam are well absorbed by the intramuscular route (20) and the latter, consistently producing effective sedation and lack of recall, may well be considered the outstanding intramuscular premedicant now available.

The benzodiazepines are widely utilized intravenously to produce sedation but not for induction of anesthesia. They are unsatisfactory as induction agents for routine clinical use because of delay in onset of action, unpredictable and wide variation in response from patient to patient, and prolonged recovery. Following intravenous lorazepam, for example, there is a delay of 10 minutes before loss of the eyelid reflex, and peak effects do not occur for 40 minutes (12). Of the drugs in this class currently available, only diazepam is used for induction of anesthesia in situations where barbiturates are contraindicated. Midazolam, a new short-acting water-soluble benzodiazepine, is undergoing extensive clinical trials in the United States and appears to be a superior alternative to diazepam as an induction agent (21).

Adverse Reactions

The most common side effects of benzodiazepine administration are extensions of expected pharmacologic actions. In relation to anesthesiology, however, three complications are of importance: prolonged somnolence, pain on injection, and venous complications.

Prolonged postoperative somnolence may be encountered when large doses are administered intraoperatively. Physostigmine 1 mg intravenously appears to be an effective antidote (22). A prolonged response is common both in the elderly and in patients with acute or chronic parenchymal liver disease (23). The dose must be reduced for such patients.

Pain on injection and venous complications are common sequelae of intravenous diazepam but are rare with flunitrazepam or lorazepam (24). Postoperative thrombophlebitis associated with intravenous diazepam is a major cause of patient dissatisfaction. Venous irritation may be due to diazepam precipitations penetrating the vein wall and is influenced in degree by the size of the vein utilized, the rapidity of injection, and the nature of the solvent (25, 26). Rapid injections and the use of small veins are associated with a high incidence of complications. The precise incidence is difficult to determine because in many reports, the study vein is subsequently used for other agents or intravenous fluids and the duration of followup may be inadequate.

Venous complications following the administration of benzodiazepines are often delayed, the incidence of phlebitis and thrombosis after 7 to 10 days exceeding that observed at 2–3 days (25).

The traditional preparation of diazepam (Valium) utilizes propylene glycol as a solvent. In an attempt to reduce venous complications, alternative vehicles have been developed. Glycoferol maintains diazepam in aqueous solution, but this preparation (Apozepam) has not been successful (27). Cremophor EL preparations commonly cause pain on injection but are associated with a much reduced incidence of thrombophlebitis. Unfortunately, Cremophor EL provokes severe anaphylactic reactions in 4% of patients (28).

Diazemuls consists of diazepam dissolved in soybean oil and emulsified in water by means of acetylated monoglycerides and egg yolk. This solvent, developed in Sweden, is similar to the fat emulsion used for intravenous nutrition (29). Olesen and Huttel (29) found that Diazemuls caused pain on injection in only 1% of cases and thrombophlebitis in 4%. For the propylene glycol preparation, the incidence of pain was 78% and the incidence of thrombophlebitis, 48% (29). In 1981, investigators in Finland reported thrombophlebitis in only 2.2% of patients receiving intravenous Diazemuls into superficial veins of the hand; the followup observation period was 14 days (30). Such findings have recently been confirmed by Kawar and Dundee, who found pain on injection and venous sequelae virtually absent when Diazemuls was used (31). Midazolam is also an excellent drug in this respect (31).

Use in Obstetrics

Benzodiazepines have been used during labor to reduce anxiety and emotional distress. Additional advantages claimed for diazepam include relaxation of pelvic musculature, the facilitation of hyperventilation control, and amnesia.

However, diazepam has been associated with neonatal hypotonia and hypothermia (32), and a relationship between neonatal plasma diazepam concentrations and neonatal distress has been demonstrated (33). In a recent study, diazepam was detected in neonatal blood 0.5 minute following intravenous administration of 10 mg to the mother just before delivery, and an inverse relationship was found between rectal temperature of the newborn and the concentration of diazepam in umbilical cord blood (34).

Diazepam crosses the placental barrier rapidly and at delivery its plasma concentration may be greater in the newborn than in the mother. The full-term neonate metabolizes diazepam easily but the principle metabolite, n-desmethyldiazepam, is both pharmacologically active and long lived. For these reasons, diazepam must be used with caution during labor. Lorazepam does not cross the placental barrier as rapidly as diazepam and does not appear in high concentrations in the neonate (35). There are no active metabolites of lorazepam; this agent may therefore prove more useful.

Use in Neurosurgery

The benzodiazepines decrease cerebral metabolism, cerebral blood flow, and intracranial pressure, but clinical experience with these drugs in neurosurgical patients who have elevated intracranial pressure is not extensive.

Diazepam has been shown to reduce cerebral blood flow in rats (36) and in a group of patients with head trauma (37). Transient decreases in intracranial pressure in normotensive but not in hypertensive neurosurgical patients were found after 0.25 mg/kg intravenous diazepam (38). It would appear that clinical doses of diazepam do not increase intracranial pressure.

Lorazepam reduces cerebral blood flow and metabolism in monkeys without significant changes in arterial blood pressure or blood gas levels; its prolonged action may be useful for some patients (39).

In dogs, midazolam affords a degree of cerebral protection similar to barbiturates (40). Midazolam reduces cerebral blood flow and increases cerebrovascular resistance in humans (41); it may therefore be used as an alternative induction agent to thiopental in patients with raised intracranial pressure.

Use in Eye Surgery

It is well established that succinylcholine given intravenously to facilitate tracheal intubation causes a transient rise in intraocular pressure which may provoke vitreous loss in the presence of an open eye. Many techniques have been advocated to prevent this rise, and gallamine and d-tubocurarine have commonly been employed. However, the efficacy of pretreatment with nondepolarizing muscle relaxants in preventing the rise in intraocular pressure following the administration of succinylcholine is doubtful (42). Pretreatment with diazepam 0.1 mg/kg intravenously reduces resting intraocular pressure and limits the increase in pressure following succinylcholine (43). Diazepam given by the oral route does not cause significant changes in intraocular pressure (44). Oral diazepam can therefore be safely given to patients undergoing ocular surgery in whom changes in intraocular pressure are undesirable.

Other Uses

Succinylcholine-Induced Myalgia. Small doses (0.05 mg/kg) of diazepam given intravenously four to five minutes before succinylcholine were found by Eisenberg, Balsey, and Katz (1979) to reduce the incidence of muscle fasciculation, the rise in serum potassium, and the incidence of postoperative muscle pain (45). The usual postoperative rise in creatine phosphokinase levels was not prevented. In a more recent study, the incidence of postoperative myalgia was 48% in controls but 17.2% in those patients given diazepam in a range of 5 mg to 20 mg intravenously as pretreatment before succinylcholine (46). The effect of 5 mg was not significant, that of 10 mg significant, but the best results were obtained with higher doses.

Pretreatment with diazepam may be considered an alternative to precurarization for the prevention of postoperative myalgia. The effect of benzodiazepines on the neuromuscular junction is not yet understood and may be fully or in part related to the solvents in which they are prepared.

Esophageal Sphincter Pressure. The tendency to regurgitate is related to the difference in pressure between the high-pressure zone of the lower esophageal sphincter and the gastric pressure. This barrier pressure is decreased by many premedicants, such as morphine or meperidine, but the effect of diazepam is uncertain. In 1981, a random double-blind study indicated that oral diazepam 10 mg decreased barrier pressure by a small but significant extent; the effect persisted, with marked variation of action, for one hour after administration (47). The same effect has been found after intravenously administered diazepam, but flunitrazepam appears to increase lower esophageal sphincter tone by an unknown mechanism (48).

The safety of diazepam as a premedicant with respect to the risk of regurgitation, hitherto unquestioned, is now in doubt (48).

Midazolam

Midazolam is a new water-soluble benzodiazepine now undergoing extensive trials. This drug is nonirritant, rapidly redistributed with a short half-life of two hours, and has only inactive metabolites (49). Administered intramuscularly, it is pain-free and produces sedation in 15–20 minutes, with a peak effect 30–45 minutes after injection (50). It has been found satisfactory for intravenous induction of anesthesia, offering more rapid onset, shorter duration, and more rapid recovery than diazepam (51). Intravenous injection is not painful. The dose required for induction is 0.2–0.3 mg/kg, but there is wide variability in response to intravenous midazolam typical of the benzodiazepines (49, 50). During induction of anesthesia, a delay may occur between loss of the eyelid reflex and loss of response to commands (51). The respiratory depressant effects of midazolam are similar to those of diazepam (52). Midazolam has little effect on the cardiovascular system and is a useful induction agent for patients with ischemic heart disease (53).

Midazolam does not cause thrombophlebitis to any significant degree, and this is its major advantage. It is likely that the future within the benzodiazepine class lies mainly with water-soluble drugs, such as midazolam, or new nonirritant preparations of diazepam.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Continuous Intravenous Infusion

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Abstract

The criteria for drugs used for infusion anesthesia are defined, and an index of equipotency, the minimum infusion rate (MIR) is defined as the steady-state infusion rate of an intravenous drug required to prevent response to an initial surgical incision in 50% of subjects. This index is comparable to minimum alveolar concentration (MAC) for gaseous or volatile anesthetics. The pharmacological characteristics and pharmacokinetic profiles are compared for five intravenous anesthetics: methohexital, Althesin, minaxolone, di-isopropyl phenol, and etomidate.

Most short-acting intravenous anesthetics were introduced into clinical practice as alternatives to thiopental for induction of anesthesia. More recently, new agents with appropriate pharmacokinetic profiles have been used for repeated incremental dosage to supplement nitrous oxide for short surgical procedures, or as a continuous infusion for longer procedures. For the latter purpose, the intravenous anesthetics have been used alone, or in combination with other intravenous drugs such as narcotic analgesics or muscle relaxants, to provide a balanced intravenous anesthetic technique. Alternatively, infusions of intravenous anesthetics have been used to supplement nitrous oxide.

Intravenous Infusion Anesthesia

The agents in common use for intravenous anesthesia are classified in Table I, which also includes information on their pharmacokinetic profiles. Notable exceptions from this classification are drugs which may be considered as supplemental to intravenous techniques but which cannot be used *alone* to provide surgical anesthesia. These are the benzodiazepines, butyrophenones, phenothiazines, and other similar drugs. In this respect the true intravenous anesthetics are akin to the gaseous or volatile anesthetics in common use, which, with the exception of nitrous oxide, can provide full surgical anesthesia without the addition of any other agent.

Minimum Infusion Rate. Potency of the gaseous or volatile anesthetics is normally determined by constructing dose-response curves, whose mid-point, ED_{50}, is synonymous with minimum alveolar concentration (MAC) (1). Prys-Roberts (2, 3) proposed that a similar index of equipotency should be adopted for intravenous anesthetics which would not only allow comparisons to be made between one intravenous anesthetic and another, but which would be directly equivalent to MAC for volatile and gaseous agents. The minimum infusion rate (MIR) of an intravenous anesthetic is defined as the infusion rate which, *when a steady state has been established,* will suppress the initial response to a surgical skin incision in 50% of patients.

Minimum infusion rates are normally determined by probit dose-response curves based on the effects of not less than five different infusion rates (4). MIR can be influenced, as can MAC (5), by age, premedication, and preexisting disease and drug therapy. When intravenous anesthetics are infused in combination with nitrous oxide the MIR is reduced to about 50%–60% of the true MIR. Table II shows the experimentally determined values of MIR for five intravenous anesthetics in humans, together with estimated values under conditions in which limited experimental data are available.

Apparatus for Delivery. For experimental pur-

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TABLE I

Intravenous Anesthetics and Their Pharmacokinetic Profiles

		Reference No.	Solvent	Mode of Administration	Elimination Half-life min	Volume of Distribution L/kg	Plasma Clearance ml/kg/min
Barbiturate	Methohexital	(11)	W	B	240	2.1	9.9
		(10)	W	I	97	1.1	12.1
Steroid	Althesin (Alphaxolone)	(3)	C	B	34	1.4	21.1
		(16)	C	I	91	1.5	10.9
	Minaxolone	(18)	W	B	47	1.6	26.0
		(16)	W	I	87	2.2	17.4
Imidazole	Etomidate	(29)	P	B	270	4.5	11.7
		(25)	A	I	—	—	20.9
Hindered Phenol	Di-isopropyl phenol	(31)	C	B	55 (cat)	—	—
		(17)	C	I	90	3.57	39.6

Key: W—aqueous solution; A—alcoholic solution; P—propylene glycol; C—Cremophor EL; B—bolus injection; I—continuous infusion.

poses, accurately calibrated syringe pumps have been used, but for infusions in clinical conditions the anesthetics may be given by infusion pumps such as the IVAC (IVAC Corporation, San Diego, CA) or from a burette giving set using an accurate drip-counter. Many of the solutions in current use have significantly different viscosities and surface tensions from water and this may markedly influence drop size in both normal and pediatric burette giving sets.

Intravenous Anesthetics

One of the main desirable characteristics of volatile and gaseous anesthetics is lipophilicity allied to low solubility in blood. Lipophilic drugs have a high affinity for neural membranes, a desirable feature in terms of uptake and elimination from the brain. Lipophilic intravenous anesthetics are frequently poorly soluble in aqueous media, and many of the drugs are formulated in oily solvents such as polyoxyethylated castor oil (Cremophor EL), propylene gycol, or dilute ethanol. Because some of these solvents have been associated with hypersensitivity responses in both experimental animals and humans, many of these agents have not hitherto been widely available in the United States, although they have been extensively studied in Europe. For this reason, methohexital, a drug freely available in the United States, is given prominence in this review, in which it is compared with four other anesthetics: Althesin, minaxolone, di-isopropyl phenol, and etomidate.

Methohexital. Numerous papers have described the use of methohexital by infusion alone or to supplement nitrous oxide for both general and neurological and dental surgery (6–8). Infusion rates in most of these studies varied between 30 and 90 μg/kg/min, dependent on the chosen premedication, inspired gas composition, and the concurrent use of narcotic analgesics. None of these studies was designed to define an ED_{50}; indeed, interest in methohexital as an infusion drug has only recently been rekindled (4, 9).

Early studies of the pharmacokinetics of sub-

TABLE II

Minimum Infusion Rates (ED_{50}) of Intravenous Anesthetics With or Without Nitrous Oxide (μg/min/kg body weight)

	With 67% nitrous oxide					No nitrous oxide	
		Premedication				Premedication	
	None	Diazepam*		Morphine†		None	Morphine
	ED_{50}	Ed_{50}	ED_{95}	ED_{50}	ED_{95}	ED_{50}	ED_{50}
Methohexital	88_E	66	81	49	76	—	—
Althesin (Alphaxolone)	25	19	25	14	18	50_E	30_E
Minaxolone	20_E	—	—	11	—	—	—
Etomidate	—	10	—	—	—	—	—
Di-isopropyl phenol	87	—	—	51	72	—	—

* Diazepam 0.15 mg/kg oral 90 min before anesthesia. † Morphine 0.15 mg/kg im 60 min before anesthesia.

anesthetic doses of methohexital by infusion in volunteers (10) indicated a short elimination half-life (97 min) and a high plasma clearance (12 ml/kg/min). Such a profile should make the drug highly suitable for infusion; one would predict that little accumulation of the drug would occur over a period of one to six hours. More recent studies of single anesthetic doses of methohexital (2.8 mg/kg) have indicated a rather longer elimination half-life (240 min), despite a similar value (9.9 ml/kg/min) for plasma clearance (11).

Based on probit dose-response curves, Sear et al (4) determined the minimum infusion rate of methohexital to supplement 67% nitrous oxide in patients premedicated with either intramuscular morphine 0.15 mg/kg or oral diazepam 0.15 mg/kg. Following morphine premedication, the MIR was 49 μg/kg/min, compared with 66 μg/kg/min following premedication with diazepam.

Infusion of methohexital at 60–65 μg/kg/min to supplement 67% nitrous oxide was compatible with surgical anesthesia supported by either spontaneous or controlled ventilation (9). During steady-state anesthesia without the influence of surgical stimulation, arterial pressures were decreased to 67% of awake values (Figure 1), associated with a 25% decrease of cardiac output and a 12% decrease of systemic vascular resistance (SVR). Surgical stimulation restored arterial pressures toward normal, largely as a result of increased SVR. Doubling the infusion rate to 120 μg/kg/min caused minimal hemodynamic changes, during either spontaneous or controlled ventilation.

Recovery from methohexital infusion anesthesia is, to some extent, dependent on the total dose administered. Thus a short infusion at a high rate may be associated with a longer recovery than a long infusion at a low rate. For infusions lasting between 2 and $4^{1}/_{2}$ hours at a rate of 60–65 μg/kg/min, the median recovery times were 20 min (range 15–40 min) for response to command, and 28.5 min (range 21–50 min) for recall of date of birth. Recovery to recall of date of birth has been strongly correlated with total dose of methohexital and with duration of infusion.

Infusion of methohexital for up to 4 hours was not associated with evidence of hepatic dysfunction (9).

Althesin. A number of steroid anesthetics have been developed following Selye's discovery (12) that pregnanedione and other naturally occurring steroids cause general anesthesia in animals. Althesin is a mixture of two steroids, alphaxolone (9 mg/ml) and alphadolone acetate (3 mg/ml) formulated in an oily solvent, Cremophor EL. Because this solvent has not been approved by the Food and Drug Administration, Althesin is not at present available in the United States. A new formulation is being developed which may make the drug acceptable for use in the United States.

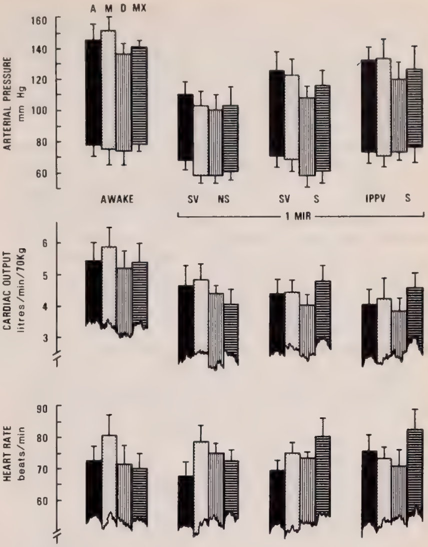

FIG. 1. Hemodynamic changes during intravenous anesthesia in patients receiving Althesin (A), minaxolone (M), di-isopropyl phenol (D) or methohexital (Mx) to supplement nitrous oxide (67%). Events were recorded in awake patients, during anesthesia before surgery (SV NS), during surgery with spontaneous (SV S) or controlled (IPPV S) ventilation, all at 1 MIR. From Prys-Roberts (30) by courtesy of the Editor of *Acta Anaesthesiologica Scandinavica*.

The pharmacokinetics of Althesin administered by infusion have been widely studied in normal patients (3), those with hepatic dysfunction (13), and hypertensive patients under treatment with β-adrenoceptor antagonists (14). When Althesin is infused at rates between 18 and 90 μg/kg/min there is a linear relationship between the plasma concentration of alphaxolone and the infusion rate, although the plasma concentration is only doubled for a fivefold increase of infusion rate. In patients with hepatic cirrhosis the mean plasma concentration of alphaxolone is lower, for a given infusion rate, than in normal patients (3, 13). This reflects a greater volume of distribution, altered protein binding, and induction of the mixed-oxidase enzyme system which is responsible for the first step in the metabolic biotransformation of the steroids. Thus, although the steroids are almost entirely dependent on hepatic hydroxylation and glucuronide conjugation for the termination of this action, there is ample reserve of this function even in severe liver disease. Althesin has been found to be a particularly useful anesthetic in these patients.

Recovery after an infusion of Althesin is rapid and pleasant. Awakening occurs at a plasma concentration of 0.9 μg/ml, approximately 50% of the plasma concentration for surgical anesthesia. The times to recovery of response to command (12 min) and to recall of date of birth (26 min; range 12–50 min) are both shorter than following an infusion of methohexital of equal duration and equivalent depth of anesthesia.

Like methohexital, an infusion of Althesin to supplement nitrous oxide caused a 24% decrease of arterial pressures (Figure 1), associated with decreased cardiac output (−11%) and systemic vascular resistance (−9%). With increasing infusion rates, arterial pressure declines progressively, though cardiac output is well maintained (15).

Minaxolone. Minaxolone, a water-soluble steroid by virtue of the di-methyl amino radical at the 11- position on the phenanthrene nucleus of the steroid molecule, was introduced in 1977 for clinical investigation in the United Kingdom, Canada, and Australia. In most respects, its pharmacological actions were very similar to those of Althesin (Figure 1) and only its hydrophilic qualities ensured a slightly different pharmacokinetic and pharmacodynamic profile (16–18). The hydrophilic quality was a disadvantage, however, because the high partition coefficient between brain and plasma contributed to slow recovery despite rapid elimination of the drug from the plasma (19). Minaxolone was withdrawn from clinical investigation in 1979 for further toxicological evaluation, but may be reintroduced in the near future.

Di-isopropyl Phenol. The agent 2-6 di-isopropyl phenol (Disoprofol) is one of a number of alkylated phenols investigated for their anesthetic properties. The term "hindered" phenol relates to the stabilizing effect on the molecule of the two isopropyl radicals around the hydroxyl radical of phenol. Like the Althesin steroids, di-isopropyl phenol is insoluble in water, and is currently formulated in Cremophor EL. This drug is still undergoing clinical trials in the United Kingdom.

Di-isopropyl phenol has been infused alone, and to supplement nitrous oxide, to provide surgical anesthesia. Used alone, an infusion of 200 μg/kg/min would appear to be necessary (19), whereas with 67% nitrous oxide, in morphine premedicated patients, the minimum infusion rate is 51.3 ± 3.8 μg/kg/min (17). Without premedication, the MIR is 87 μg/kg/min (20).

The hemodynamic effects of di-isopropyl phenol (21) during spontaneous or controlled ventilation, before or during surgery, were similar to those observed for methohexital, Althesin, and minaxolone (Figure 1).

Recovery following an infusion of di-isopropyl phenol is particularly rapid, the median times for both response to command and recall of date of birth being within 7 minutes.

Etomidate. Etomidate, an imidazole derivative, was introduced for induction of anesthesia in 1977 (22), and has been widely used in continuous infusion as an intravenous anesthetic in combination with fentanyl (23, 24, 25), and as a sedative in intensive care units (26). Because of its minimal effects on the circulation when given as an induction agent (27), etomidate has been recommended for use as a continuous infusion agent in patients with cardiovascular disease.

Following rapid induction with an infusion of 100 μg/kg/min for 10 minutes, stable anesthesia can be achieved with a continuing infusion at 10 μg/kg/min supplemented by fentanyl 5–10 μg/kg. Under these conditions mean plasma concentration of 0.52 μg/ml was achieved, indicating fast clearance (20.9 ml/kg/min) of the drug from the plasma (25), a value similar to that obtained after single bolus injections (28, 29). A similar infusion technique (24) resulted in slightly lower plasma concentrations (0.33 ± 0.1 μg/ml).

Recovery from etomidate infusions is comparable to that after the other intravenous anesthetics (25); reported median times to response to command and to recall of date of birth are 9.8 and 18.5 min respectively. No hepatic dysfunction has been found following infusions of etomidate (25).

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Ketamine

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The search for a new intravenous induction and maintenance anesthetic agent has been stimulated by numerous untoward medical effects (1–5) and the rising costs of volatile anesthetic agents. Volatile agents are currently undergoing many clinical investigations surrounding their effects on organ subsystems, principally in the liver (2, 4–7). Furthermore, the potential hazards of operating room pollution on the staff and their offspring (8, 9) has intensified the clinical introduction of new intravenous anesthetic agents.

Ketamine was first synthesized by Stevens in 1963 (10). Initial clinical studies with ketamine on human volunteers were reported by Domino et al (11). Five years later, in 1970, the drug was approved for general clinical administration.

Ketamine (CI-581, Ketalar or Ketaject) (12) has a chemical structure [2-(0-chlorophenyl)-2-methylamino cyclohexanone] which resembles cyclohexamine and phencyclidine. Ketamine has a molecular weight of 238, and is a water-soluble, acid crystalline compound. It is a rapid and smooth-acting anesthetic agent when administered intravenously or intramuscularly. Metabolism is rapid. The biotransformation, biodisposition, pharmacokinetics, and metabolism of ketamine are well established (13–16).

Pharmacology

Central Nervous System. Ketamine produces "dissociative" anesthesia: it appears to selectively interrupt association pathways of the central nervous system. It may selectively depress the thalamoneocortical and limbic systems. This state is characterized by catalepsy, sedation, amnesia, and analgesia. White et al (17, 18) have described ketamine anesthesia in detail. On electroencephalogram, it induces increased alpha, delta, and theta waves, but no change in beta waves. Ketamine increases cerebral blood flow and intracranial and cerebrospinal fluid pressures. It may produce nystagmus and diplopia (19).

Its postanesthetic emergence phenomena include immediate postoperative effects of excitement, delirium, disorientation and other psychic conditions, and later complications, hallucination and vivid or weird dreams. Psychic disturbances after ketamine anesthesia have been reported to occur in about 15% of adult cases (20). Several reports (21–25) have indicated that premedication with diazepam, or the concomitant intravenous administration of diazapem during induction, markedly decreases these untoward reactions. Lorazepam has also been shown to have such protective action (26). With diazepam and lorazepam, the incidence of emergence phenomena is less than 1% (20).

Ketamine produces profuse salivation and lacrimation, which can be prevented by atropine (18).

Cardiovascular System. The cardiovascular effects of ketamine in general are stimulatory. It increases blood pressure, heart rate, and cardiac output, although effects on stroke volume and systemic vascular resistance are variable (19, 27). It has been suggested that the stimulatory effects are centrally mediated via the sympathetic nervous system (28). On the basis of its cardiovascular stimulatory effects, ketamine has been widely advocated as the drug of choice for the severely ill patient (29, 30). Ketamine, according to some observations, increases pulmonary artery pressures and pulmonary resistance (31).

Hypertension and tachycardia associated with the use of ketamine can be avoided by the concomitant administration of diazepam and droperidol (24, 25, 30, 32, 33).

Respiratory System. The respiratory effect of ketamine appears to be minimal and transient. Mild depression has been found by some authors, but others have reported respiratory stimulation (19, 34). Patients premedicated with diazepam, anesthetized with ketamine 2 mg/kg, and

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breathing air, showed no significant changes in PaO_2 and $C(a\text{-}v)O_2$ (35). There were no significant changes in maternal and infant arterial blood gas values when an intravenous infusion of ketamine 1 mg/kg was used for vaginal delivery (36). Corssen and others (19, 37) have reported that ketamine is safe for administration to asthmatic patients, and that it produces relief from bronchospasm (38). Coughing and laryngospasm rarely occur with ketamine, and laryngeal reflexes are not depressed during anesthesia (19).

Other Subsystem Effects. Studies in healthy volunteers of liver function after administration of ketamine showed no changes in enzyme and bilirubin concentrations (19). Ketamine increases muscle tone and may cause involuntary jerky movement of large muscle groups (11). It can be safely used in patients with myopathies or malignant hyperthermia (19, 39–41).

Considerations for the clinical use of ketamine include the following (asterisk indicates that our own clinical experience is discussed in the section below titled "Clinical Experience"):

Pediatric anesthesia (18, 19, 34, 47–51)
- Induction: intramuscular-route patients not properly sedated with premedication; unpremedicated outpatients prior to insertion of an intravenous catheter.
- Induction and maintenance: any surgical procedure; widely used for diagnostic procedures—endoscopy, radiology, cardiac catheterization,* oral surgery.

Geriatric anesthesia (18)

Critically ill and poor-risk patients (29, 30, 52)
- Shock or cardiogenic shock.*
- Severe anemia, dehydration.
- Constrictive pericarditis and cardiac tamponade.
- Respiratory dysfunctions.
- Burn trauma.
- Short procedures: surgical, dressing changes, drainage.

Supplement to local and regional anesthesia (18)
- When surgical procedure is prolonged.
- When block is not sufficient.

Special indications
- Bronchial asthma (37, 38).
- Intermittent porphyria (53).*
- Malignant hyperpyrexia (39, 40, 41).

Obstetrical anesthesia (18, 36, 54, 55)

Outpatient anesthesia (56, 57)

One-lung anesthesia (32, 33, 58, 59)*

Ketamine anesthesia for abortion may reduce the blood loss during the procedure due to an increase of uterine tone and contractions (42, 43). There are extensive studies on ketamine's effect on the pregnant uterus (44, 45).

Renal function is not affected directly by ketamine (19), nor are renin serum levels increased (46) by it.

Clinical Applications of Ketamine

Ketamine has broad areas of application. The different indications for its use as an analgesic, sedative, or anesthetic allow for schematic applications in clinical practice (a) as the sole anesthetic agent for diagnostic and short surgical procedures, or as a supplement to local and regional anesthesia; (b) for induction of anesthesia (intramuscular or intravenous) prior to the use of other anesthetic agents for maintenance; (c) to supplement low-potency anesthetic agents such as nitrous oxide; (d) combined with diazepam or lorazepam premedication, or used concomitantly for induction; (e) for maintenance of anesthesia by continuous drip (using an IVAC 530 microinfusion pump, IVAC Corp., San Diego, CA) supplemented by nitrous oxide. If endotracheal intubation is indicated, a muscle relaxant is used. Ketamine administration permits the use of 100% oxygen when this is beneficial, for example in cases of anemia and critical illness.

The continuous infusion technique of administering ketamine permits the anesthesiologist to titrate the drug and minimize peaks and valleys in depth of anesthesia. This technique results in excellent, stable anesthesia for major surgical procedures (18, 19, 24, 32). The continuous-drip infusion technique reduces the amount of ketamine administered, thereby reducing side effects (33).

In elderly patients, ketamine is widely used, not only in the operating room, but also in critical care units and for minor surgical intervention, drainage, and similar procedures (29, 30). Reves (52) reported the advantages of ketamine in patients with cardiac tamponade and constrictive pericarditis. Diazepam-ketamine administration in this type of patient increases the arterial and right atrial pressures, but does not affect wedge pressure or the cardiac index. Rises in blood pressure may increase perfusion, but may also increase afterload and thereby decrease cardiac output. These patients already have compensatory tachycardia, so no increase in heart rate is seen. Ketamine is widely used for general pediatric and pediatric cardiac anesthesia. It is used both for induction and maintenance (49, 50).

Clinical Experience

Cardiogenic Shock. Hatano et al (60) reported that anesthesia was smooth and simple, with minimal effects on hemodynamic function, in patients undergoing open heart surgery when ketamine was administered by continuous infusion in combination with diazepam and nitrous oxide. After clinical confirmation of his study, we used only ketamine (2 mg/kg for induction and 3 mg/kg/hour for maintenance) in 16 patients in cardiogenic shock (15 patients underwent coronary artery bypass graft surgery and 1 underwent pulmonary embolectomy). All 16 patients were on vasoactive pharmacological agents. Nine had an intra-aortic balloon pump inserted prior to induction or cardiac catheterization, and four had suffered cardiac arrest. All patients were conscious and required anesthesia. Only ketamine and muscle relaxants were given for induction and maintenance. There were no significant hemodynamic changes (mean arterial blood pressure ±15 torr and heart rates ±10/minute) from induction to the period when the patient was connected to cardiopulmonary bypass.

Cardiac Catheterization. Extensive clinical data using ketamine for cardiac catheterization in pediatric patients have shown this agent to be satisfactory (48, 51). Hemodynamic changes are transitory and are barely detectable after 15 minutes (51). Dillon (61) and Coppel and Dundee (34) reported fewer dysrhythmias during manipulation with the catheter or injection of the contrast media during ketamine anesthesia.

We use ketamine for cardiac catheterization. After premedication (atropine and diazepam in children with body weight over 20 kg), induction is achieved with ketamine 5–10 mg/kg intramuscularly or 2–3 mg/kg intravenously. For maintenance we have found a continuous microinfusion of ketamine 2–4 mg/kg/hour by IVAC pump satisfactory.

Intermittent Porphyria. The literature relating to the safety of intravenous induction agents in patients with acute intermittent porphyria is sparse. Barbiturates are contraindicated. Our experience with ketamine has been uneventful, but is limited (53).

One-Lung Anesthesia. When endobronchial one-lung anesthesia is employed, the anesthetic regimen for maintenance during collapse of the operative lung has usually consisted of high concentrations of oxygen with volatile anesthetic agents. This technique has been associated with significant arterial hypoxemia in 15%–25% of cases (32, 62, 63). Factors contributing to hypoxemia during one-lung anesthesia include increased true intrapulmonary shunting, ventilation-perfusion abnormality, and reduction of cardiac output (59).

The major cause of hypoxemia during one-lung anesthesia is persistence of blood flow through the unventilated lung. Hypoxic pulmonary vasoconstriction is normally an important mechanism for reducing the amount of blood flowing through the unventilated lung. Several reports have focused attention on the reduction or abolition of hypoxic vasoconstrictive reflexes in the collapsed lung by most of the volatile anesthetic agents (58, 64, 65). This response is not abolished by intravenous anesthetic agents (58).

Following experimental studies on dogs (58) which demonstrated the superiority of ketamine over halothane, we used ketamine for thoracic cases. One hundred and fifty patients undergoing elective thoracotomy for pulmonary resection were anesthetized as summarized below. The technique was described in 1980 (32, 33, 58, 59).

The patients were premedicated one hour prior to surgery with oral diazepam 10–20 mg and atropine 0.6 mg intramuscularly. At the operating suite, monitoring was established with EKG, arterial line (for mean arterial blood pressure and blood gases) and, in selected cases, Swan-Ganz catheter. Anesthesia was induced intravenously with diazepam 10 mg, droperidol 5 mg, and ketamine 2–3 mg/kg. Muscle relaxation was achieved with d-tubocurarine 30–45 mg, and patients were ventilated by mask until endobronchial intubation was performed with a Carlens or a Robertshaw double-lumen tube. This sequence of medication did not provoke tachycardia or hypertension in most patients.

Anesthesia was maintained throughout the procedure with a continuous intravenous infusion of ketamine 2–4 mg/kg/hour, using an IVAC pump. Patients were ventilated with 50 percent O_2 in N_2O delivered by an Engstrom ventilator. During one-lung anesthesia, the same tidal volume was used for both lungs. Once the patient was stabilized (10 minutes) on two-lung and then on one-lung anesthesia, blood samples were taken for blood gases (and shunt) determination. At the end of the procedure, the patient was reintubated with a single-lumen endotracheal tube, and residual relaxation was reversed. Early extubation was performed in the intensive care unit, depending upon ventilatory parameters and arterial blood gases.

Detailed results have already been published (32, 59). With F_1O_2 0.5 on one-lung ventilation, mean PaO_2 was 84 torr, and the calculated shunt fraction was 25.9%. During one-lung halothane anesthesia with F_1O_2 0.5, 32 of 80 patients had PaO_2 below 70 torr, compared with 5 of 150 patients who received ketamine (59).

Ketamine provides a superior alternative to halothane for one-lung anesthesia. White et al (18) recently described the contraindications to the use of ketamine: (a) cardiovascular disease; (b) central nervous system disorders; (c) open globe injury to the eye or increased intraocular pressure; (d) thyrotoxic states; (e) otolaryngological procedures; (f) psychiatric disorders or history of adverse reaction to ketamine.

Summary

Ketamine is a rapidly acting, safe parenteral analgesic and anesthetic agent which has been in worldwide clinical use since 1970. New derivatives have been synthesized and appear promising. Phencyclidines that lack the psychotropic effects of ketamine and do not induce tachycardia and hypertension may become available in the near future.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Narcotics

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Among the milestones in the history of narcotic analgesic anesthesia are the following events:

300 BC	First recorded use of *Papaverum somniferum* as a source of pain-relieving medicinals.
1803	Serturner isolates morphine from opium.
1850	Morphine premedication used for ether anesthesia (Bruno).
1869	Morphine reduces the concentration of chloroform required for anesthesia (Claude Bernard).
1900	Morphine-scopolamine "anesthesia" abandoned.
1969	Morphine anesthesia used for cardiac surgery (Lowenstein et al).
1978	Fentanyl anesthesia used for cardiac surgery (Stanley et al).

How Morphine Meets the Objectives of Anesthesia

1. **Analgesia** of a profound degree is possible.
2. **Unconsciousness** occurs in debilitated patients. **Sleep** occurs in physically fit individuals, but they remain arousable to intense stimulation even after doses of more than 3 mg/kg. Morphine alone does **not** produce **amnesia**.
3. **Muscular relaxation** is **not** produced by morphine; under certain conditions muscular tone increases to the point of rigidity.

Hemodynamic Stability. Hemodynamic stability is of special concern in the patient with cardiovascular disease. The reintroduction of morphine anesthesia in the 1960s was based on the observation of minimal hemodynamic changes when this narcotic analgesic was administered to critically ill patients under intensive care. The lack of myocardial depression makes morphine a useful alternative to halothane and other potent inhalational anesthetics in the patient with compromised cardiac performance (for example, valvular heart disease). Hypotensive episodes related to bradycardia, histamine release, and other actions of morphine are easily treated, since morphine does not interfere with the actions of autonomic agonists and antagonists.

The major limitations of morphine as an anesthetic became apparent with the advent of aortocoronary artery bypass operations in otherwise physically fit patients with good ventricular function. Doses large enough to render these patients unconscious and to suppress their sympathetic and hemodynamic responses (tachycardia, hypertension) to noxious stimulation produced not only hypotension but also severe degrees of edema and prolonged coma (1, 2).

Fentanyl has become the currently accepted alternative to morphine mainly because it can be used in doses equivalent to morphine doses of 8 mg/kg or more without producing such marked degrees of hypotension, edema, or coma. (Dr. Stanley discusses fentanyl anesthesia in his article, and Dr. de Lange discusses the anesthetic uses of new derivatives of fentanyl.)

Advantages of Narcotic Analgesics as Primary Agent

Minimal depression of cardiac contractility.

No sensitization of myocardium to catecholamine action.

Preservation of autoregulation of blood flow, especially to brain, heart, and kidneys.

No interference with autonomic or cardiovascular drug actions.

Early postoperative arousal of patient.

Postoperative analgesia.

Ventilatory depression facilitates mechanical ventilation.

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Suppression of cough reflexes increases toleration of endotracheal tube.

Antagonists available, but should be used cautiously (as indicated below).

No hepatic or renal toxicity.

No environmental pollution, but have high potential for abuse and can induce psychological and physical drug dependence.

Not teratogenic, but transfer to the fetus can lead to ventilatory depression and coma in the newborn.

Not a trigger of malignant hyperthermia.

Limitations and Management of Narcotic Analgesics

Awareness: nitrous oxide, diazepam, thiopental, enflurane.
Recall: scopolamine, diazepam, nitrous oxide.
Rigidity: muscle relaxants, deepen anesthesia.
Bradycardia: anticholinergic, sympathomimetic.
Hypotension: increase venous return, intravenous fluids, sympathomimetic.
Hypertension: sympatholytic, enflurane, vasodilator.
Tachycardia: propranolol, enflurane.
Ventilatory depression: mechanical ventilation, naloxone.
Nausea and retching: antiemetic.
Biliary or intestinal colic: nitroglycerin, glucagon, naloxone.

The identification of a reliable indicator of anesthetic depth in the paralyzed patient would go a long way in solving some of these problems. It would reduce the potential of awareness and later recall of intraoperative events, probably would reduce the incidence and degree of hemodynamic responses to noxious stimulation, and could make the administration of narcotic analgesics more precise and efficient, thereby reducing the duration of postoperative ventilatory depression.

Ventilatory Depression. Postoperative ventilatory depression is inherent in the use of any currently available narcotic analgesic as the primary or sole anesthetic agent because of the residual effects of the very large doses required for anesthesia. The development of shorter-acting narcotic analgesics (for example, alfentanil) and of more precise and efficient methods of administration (computer-asisted infusions, for instance) should reduce the magnitude of this problem. In the meantime, the anesthesiologist has three choices: (a) limit the dose of narcotic analgesic by supplementing it with short-acting hypnotics or anesthetics; (b) support ventilation mechanically in the postoperative period until the residual narcotic analgesic is mostly eliminated; (c) administer naloxone or another narcotic antagonist (1–3).

The last choice entails three risks: making the patient uncomfortable with pain, precipitating hypertension and tachycardia, and bringing on recurrence of ventilatory depression when the effects of the antagonist are dissipated. The antagonist will produce an acute abstinence syndrome in the patient physically dependent on any narcotic analgesic and the associated stress is dangerous to the critically ill or newborn patient.

Narcotic agonist-antagonist analgesics include pentazocine (Talwin), butorphanol (Stadol), and nalbuphine (Nubain). These drugs are characterized by limited efficacy ("ceiling effect") in CNS actions, including ventilatory depression, analgesia, and the ability to reduce the requirements for other anesthetic drugs. Therefore, the antagonist analgesics are not useful as primary or sole anesthetic agents, although they may be used to supplement other general anesthetics (3, 4).

Differences in Duration. Pharmacokinetic differences exist among the narcotic analgesics (5). Long-acting drugs include morphine and many of its derivatives (retained in the nervous system because of low lipid solubility), methadone (slow elimination from the body), and lofentanil (slow dissociation from narcotic receptors).

Intermediate duration of action characterizes meperidine (Demerol), alphaprodine (Nisentil), and fentanyl (Sublimaze) and sufentanil. Cardiac depression and CNS stimulation limit the doses of meperidine and alphaprodine to less than those required for anesthesia. Fentanyl is short-acting after small doses because its concentrations rapidly decline to below the effective range during the distribution phase, and fentanyl may be long-acting after very large doses because its concentrations remain in the effective range during its slow elimination from the body.

Short-acting narcotic analgesics need to be developed for anesthetic purposes in patients who undergo brief operations and for whom mechanical support of ventilation in the postoperative period is inappropriate. Alfentanil (Alfenta) has a rapid onset of action and is eliminated more rapidly from the body than any other currently available narcotic analgesic. Its pharmacokinetic characteristics make feasible raising and lowering its concentrations in the brain rapidly, and thereby facilitate its use under circumstances in which the intensity of noxious stimulation varies widely (6).

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

High-Dose Fentanyl

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Until the last decade narcotics (opioids) were not considered to be anesthetics. However, many recent studies have confirmed that narcotics can be anesthetics. Why has it taken so long for narcotics to be so recognized?

A likely explanation may be related to the fact that until recently narcotics, except in a few isolated circumstances, have rarely been used in sufficiently high doses to manifest their anesthetic qualities. Historically, narcotics have been considered analgesics and have only been used in doses that produce analgesia and sedation. These doses are significantly lower than doses necessary to reliably produce anesthesia. For example, morphine (10–20 mg, intramuscular or intravenous) will reliably produce analgesia in a 70-kg adult man but rarely, if ever, result in anesthesia unless supplemented with another central nervous system depressant. In order to produce anesthesia, 10–30 times as much morphine is needed. One reason why high doses of morphine (3–8 or more mg/kg) and other narcotics (meperidine, alphaprodine) were rarely used as anesthetics may be that detrimental side effects, including acute severe hypotension, anaphylaxis, and prolonged respiratory depression, are common when doses are high. Side effects seem to occur less frequently as the potency of narcotics increases. This is especially true of the potent new synthetic pure-agonist opioids but may also be true of some of the new agonist-antagonist compounds. The goal of this discussion is to briefly describe the evidence that suggests narcotics are anesthetics; the differences between narcotic anesthesia and anesthesia with other types of compounds; and advantages and disadvantages of narcotic anesthesia.

Evidence that Narcotics Are Anesthetics

The neurophysical state obtained by use of large doses of opioid analgesics is uncertain. It is not the same as the "general anesthetic" state resulting from the use of volatile inhalational agents. Opioid analgesics are more selective in action than general anesthetics, which produce dose-related generalized depression of the central nervous system. High-dose fentanyl anesthesia results in a very specific electroencephalographic response characterized by high voltage slow delta waves. A similar EEG pattern has been reported after administration of meperidine 400 mg IV. The EEG appearance with fentanyl does not alter with addition of N_2O or surgical stimulus and is consistent with deep surgical anesthesia. The EEG effects of fentanyl in doses greater than 50 μg/kg are not different from those at 50 μg/kg, suggesting that opioid analgesics act on the central nervous system in a manner different from other general anesthetics. Another feature of the general anesthetic state is the production of an increase in muscle tone sometimes resulting in "lead-pipe" rigidity, by an unknown mechanism. Neuromuscular blocking agents can be used to block this action of opioids or treat it once it occurs.

Profound analgesia, loss of consciousness, and reliable amnesia throughout operation can be achieved with many agonist narcotic compounds, provided sufficient brain and thus plasma levels are maintained. Generally speaking, the higher the dosage the more likely is complete amnesia (incomplete amnesia is occasionally reported after narcotic anesthesia). Because of the absence of data on brain and plasma narcotics concentrations necessary for anesthesia, many clinicians have avoided using these drugs without supplementation. Studies are now in progress throughout the world to provide clinicians with these data as well as information on appropriate infusion rates of new and older narcotics. At the moment the most rational way of giving most narcotics ap-

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pears to be via continuous infusion. However, good, experienced clinicians can often achieve as good results with a knowledge of narcotic pharmacokinetics and with careful monitoring of clinical signs (blood pressure, heart rate, cardiac output, peripheral resistance, pupillary size, skin color, and so on). Whether it is possible to achieve similar results using agonist–antagonist compounds without supplements is debatable. Most data suggest that the agonist–antagonist narcotics are not sufficiently potent to be used by themselves as anesthetics.

Disadvantage of Opioids in Anesthesia

Heart Rate. The intravenous injection of fentanyl produces bradycardia in humans and animals. In this respect it is similar to other opiates, with the exception of meperidine, which often causes tachycardia. Tachycardia also occasionally occurs during induction of anesthesia with morphine, usually accompanied by facial and upper torso flushing. This may be related to histamine release.

Fentanyl-induced bradycardia is more marked in the anesthetized than in the conscious human. Second and subsequent doses of fentanyl cause less bradycardia than the first dose. The degree of bradycardia after infusion of narcotics may, to some extent, be dose-related, although an equally important factor is speed of injection; bradycardia can be minimized by slow administration. Premedication with atropine can minimize but not always eliminate fentanyl-induced bradycardia. Atropine is also usually effective in treating opioid-induced bradycardia but on occasion even large doses (1–2 mg) are ineffective. The prior administration of a small (2-mg) dose of pancuronium before induction of anesthesia with fentanyl can prevent muscle rigidity and attenuate bradycardia by producing moderate tachycardia.

Blood Pressure—Hypotension. Anesthesia with morphine may occasionally be associated with hypotension, which may be severe. In one reported series involving valvular surgery, the patients had a 10% incidence of hypotension with systolic blood pressure below 70 torr. One patient sustained a myocardial infarction as a result of morphine-induced hypotension. However, morphine and halothane anesthesia produced a similar incidence of severe hypotension in this study. The mechanisms of this hypotension are unclear and are probably multifactorial. Rate of administration and underlying pathology may be important.

The development of hypotension does not appear to be associated with significant myocardial depression, although morphine (2 mg/kg) in healthy volunteers does cause prolongation of the pre-ejection period, an estimate of isovolumetric cardiac contraction. Hypotension after morphine is most probably due to decreases in system vascular resistance secondary to histamine release. Morphine causes significant reduction in venous and arterial tone in both animals and humans. The degree of venous pooling is dose-related and causes a significant increase in the amount of blood and crystalloid fluid required to maintain adequate filling pressures in patients receiving morphine 9 mg/kg as compared with those given 3 mg/kg. The vasodilation may also be due to a direct effect of morphine on vascular smooth muscle. Hypotension rarely occurs with high-dose fentanyl anesthesia, possibly because fentanyl, unlike morphine, does not cause histamine release.

Blood Pressure—Hypertension. The most common cardiovascular disturbance during high-dose fentanyl anesthesia for cardiac surgery is hypertension during or after sternotomy. The reported evidence of hypertension varies widely. Stanley et al reported no change in cardiovascular variables following surgical stimulation. Other investigators have reported incidences of hypertension specifically related to sternotomy of 45%–100% in patients given fentanyl 50–70 μg/kg. The reason for this variability between institutions is not clear. Possible factors may be rate of administration, degree of beta-adrenergic blockade present at the time of surgery, and differences between populations. In an investigation comparing fentanyl requirements in patients undergoing coronary artery surgery in Salt Lake City (U.S.A.) and Leiden (The Netherlands), it was found that poststernotomy hypertension was controlled in 90% of patients from Salt Lake City with fentanyl 75 μg/kg but was not controlled in 80% of patients with 121 μg/kg in the Dutch patients. Satisfactory blood pressure control can be achieved with extremely high doses of fentanyl (140 μg/kg). Unfortunately, doses of fentanyl of 140 μg/kg or more are likely to result in prolonged postoperative respiratory depression. Satisfactory blood pressure can be achieved with fentanyl 50 μg/kg plus vasodilator therapy. However, with such low doses of fentanyl, the risk of intraoperative awareness is probably higher than with doses over 100 μg/kg of fentanyl; at that dosage intraoperative awareness has never been reported, but has occasionally been reported with lower doses.

Hypertension during cardiovascular surgery was also a problem in patients anesthetized with morphine. Arens et al report a 36% incidence of hypertension (defined as rise in systolic blood pressure to over 200 torr or an increase of 60 torr above preoperative pressure) in patients undergoing coronary artery surgery with high-dose morphine anesthesia. Hypertension during morphine anesthesia has been variously attributed to light anesthesia and stimulation of the renin-angiotensin mechanism. These explanations, with the exception of inadequate anesthesia, do not appear to be valid in the case of fentanyl; to date, the mechanism responsible for the phenomenon is unknown, although various explanations have been suggested.

Respiratory Depression. Fentanyl, in common with the other opioids, produces dose-related respiratory depression. Both the responsiveness to carbon dioxide and respiratory rhythmicity and reflexes are affected. The maximum depression with most of the narcotics occurs within 5 minutes after intravenous injection and even with small doses of fentanyl (2–9 μg/kg), changes in CO_2 response curve can be found 3–4 hours after administration. This is in contrast with the much shorter duration of analgesia. With the higher doses of fentanyl which are used in cardiac surgery, respiratory depression can persist for many hours, and patients may have to be ventilated for 12–18 hours after induction of anesthesia. However, in my experience, many patients can tolerate extubation within 4 hours of the end of operation without marked elevation in $PaCO_2$.

Delayed respiratory depression occurring after a period of adequate respirations has been reported following small doses of fentanyl. This may be due to varying intensity of stimulation in the postoperative period. Another explanation may be the occurrence of secondary increases in plasma fentanyl concentrations during the elimination phase, possibly caused by enterohepatic recirculation, which have been described by some but not other investigators.

Opioid-induced respiratory depression can be reversed by opioid antagonists, for example naloxone. However, respiratory depression may recur. The analgesic effects will also be reversed by an antagonist.

Extreme caution must be exercised when naloxone is given to reverse the depressant effects of opioids, particularly when these have been administered in high doses. There have been several reports of intense pressor responses when naloxone has been used to reverse morphine in animals and humans and when naloxone has been administered during enflurane anesthesia. Flacke et al reported hypertension with severe pulmonary edema immediately after naloxone 0.4 mg IV to reverse morphine 136 mg given during open heart surgery. Increased myocardial irritability also occurs with ventricular fibrillation and multiple premature atrial contractions. Although these cardiovascular responses to naloxone may be partly explained by reversal of analgesia, this cannot be the complete explanation.

Muscle Rigidity. The problem of muscle rigidity associated with the use of opioids during anesthesia was first reported by Hamilton and Cullen in 1953. However, this phenomenon did not gain widespread attention among anesthesiologists until the introduction of neuroleptanalgesia. Corrsen et al reported an 80% incidence in patients receiving Innovar with a fentanyl dose of 9 μg/kg. Grell, Koons, and Denson found that single intravenous doses of fentanyl 0.5–0.8 mg consistently produced chest-wall rigidity within 60–90 sec of administration. It is characterized by increased muscle tone, progressing to rigidity, particularly involving the thoracic and abdominal muscles. Rigidity of the thoracic muscles can cause difficulties with ventilation in the nonparalyzed patient. Rapid injection increases the severity, and slow administration is therefore recommended. The concomitant use of nitrous oxide also increases severity.

The exact mechanism by which opioids produce muscle rigidity is not clearly understood. It is probably a manifestation of the catatonic state which is a basic pharmacological property of all opioids. Rigidity is not due to direct action on muscle fibers, since it can be blockaded by neuromuscular blocking drugs. It is not associated with increases in creatinine phosphokinase, suggesting little or no muscle damage occurs during the period of muscle rigidity. Opioids do not have any significant action on nerve conduction and have a minimal effect on the monosynaptic spinal reflexes associated with muscle stretch receptors. Current evidence indicates a single site of action, possibly in the caudate nucleus, and a possible relationship to opioid-induced enhancement of dopamine biosynthesis which occurs after many opioids, including fentanyl.

Awareness and Effects of Supplements. In addition to cardiovascular, respiratory, and neuromuscular problems, one of the most serious drawbacks of morphine anesthesia is the high incidence of inadequate anesthesia. Sporadic episodes of awareness occur more commonly in patients undergoing coronary artery surgery, the majority of whom do not have a history of chronic low cardiac output syndromes. In the relatively fit patient, much larger doses of morphine are required to abolish awareness and to produce adequate surgical anesthesia. Indeed, doses of up to 11 mg/kg have been required in some patients. Wong et al found that morphine 2 mg/kg given to healthy, unpremedicated volunteers did not produce amnesia or unconsciousness; unconsciousness was only achieved by the addition of 70% nitrous oxide.

Awareness and inadequate anesthesia have been much less a problem when high doses of fentanyl are used. Even small doses of fentanyl can affect patient awareness. When amnesic compounds such as diazepam or scopolamine are omitted, 50% of patients become unaware of visual stimuli at a dose of fentanyl 6–7 μg/kg. To date, there are only a few reports in the literature of awareness occurring during high-dose fentanyl anesthesia. In one report this occurred with the second but not the first of two fentanyl anesthetics administered six days apart. The total dose of fentanyl was similar in both cases (76 μg/kg), although diazepam was given during the first and not during the second anesthetic. Another report concerned a 41-year-old woman undergoing elective mitral valve replacement who was given a total dose of fentanyl 90 μg/kg. She was aware of sounds and conversation during the period of sternotomy.

A variety of supplementary drugs have been used in combination with the opioids in an effort to reduce the incidence of awareness, to control hypertension, and, by limiting the total dose of opioid required, to attenuate the extent of postoperative respiratory depression. Unfortunately, with few exceptions, the use of supplements during high-dose opioid anesthesia results in some loss of cardiovascular stability. The most common supplement used with intravenous narcotics is nitrous oxide. Nitrous oxide alone has minimal effects on cardiovascular dynamics, although it does depress myocardial contractile force in dogs. Its use in combination with high-dose opioids is associated with myocardial depression, increases in systemic vascular resistance, and decreases in cardiac output and blood pressure. This has been a consistent finding with all opioids studied, including morphine, meperidine, and fentanyl. The reasons why nitrous oxide should have such cardiovascular depressant effects in the presence of opioids are unknown, but appear not to be related to the plasma concentrations of opioids.

Diazepam, which by itself has little cardiovascular effect, similarly causes marked depression when given to patients who have received either morphine or fentanyl. Similar interactions will probably also occur with other combinations of opioids and benzodiazepines. Of other intravenous supplements which have been studied, it appears that only scopolamine and droperidol do not produce significant cardiovascular depression when combined with opioids, although droperidol may cause a fall in vascular resistance and blood pressure. The addition of low-to-moderate concentrations of halothane after large doses of morphine also produces marked cardiovascular depression in patients with coronary artery disease.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Clinical Experiences with Analogues of Fentanyl

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High-dose fentanyl anesthesia became established in seriously ill patients because it provided adequate anesthesia without cardiovascular depression and also appeared to protect against the hemodynamic and endocrine stress responses to surgery (1–3). Unfortunately, some untoward reports about fentanyl anesthesia marred the full success of this technique. These reports, which involved otherwise healthy patients undergoing coronary artery surgery, described the occasional occurrence of severe bradycardias associated with the induction of anesthesia (4), prolonged induction times with a high incidence of muscle rigidity (5), instances of awareness and recall during surgery (6), failure to block hemodynamic responses to noxious stimuli (5, 7), and incomplete suppression of the endocrine stress response to cardiopulmonary bypass (3, 8). In addition, high-dose fentanyl anesthesia resulted in postoperative respiratory depression which lasted several hours (1, 3).

Could these deficiencies of fentanyl anesthesia be minimized by using other opioids with different potencies, speed of onset and duration of action? Early in 1980 two new congeners of fentanyl, alfentanil and sufentanil, with these properties became available for investigation at the University of Leiden, The Netherlands. Following approval by the medical ethics committee and informed patient consent, investigations were carried out to assess and to compare with fentanyl the performance as sole anesthetic agents of these opioids in cardiac surgical patients.

Sufentanil. Sufentanil has five to ten times the potency of fentanyl and about twice the already large safety margin of fentanyl (9). Preliminary studies in animals and humans indicated that the action of sufentanil resembled that of fentanyl but was better in reducing the incidence of intraoperative tachycardia and hypertension (10, 11); it also appeared to result in less postoperative respiratory depression (12).

Alfentanil. Alfentanil has a comparatively rapid onset of action, with one third the potency and one third the duration of action of fentanyl (9). Initial clinical experience with alfentanil suggested that these properties, together with a minimal effect on cardiovascular dynamics, would allow considerable flexibility in its anesthetic use (13, 14).

Technique. The basic anesthetic technique used for the three opioids was the same. Following preoxygenation and precurarization (pancuronium 0.02 mg kg^{-1}), an anesthetic induction dose was given at a fixed rate until unconsciousness; this dose was then doubled by incision time. In addition, incremental bolus doses were given in response to systolic arterial pressure rises (15, 16). The rate of drug administration for induction and magnitude of incremental bolus dose of the respective opioid is shown in the table.

Induction. For patients about to undergo coronary artery surgery, both alfentanil and sufentanil afforded rapid induction of anesthesia which maintained hemodynamic stability and allowed stress-free endotracheal intubation. The anesthetic induction time was more than three times faster for alfentanil and sufentanil than for fentanyl but the incidence of concomitant muscle rigidity, 25%, was the same for all three opioids (15, 16). This rigidity could easily be counteracted with muscle relaxants. Alfentanil was also found to be suitable as an induction agent for patients undergoing major abdominal surgery because of its relatively short duration of action (17). In contrast to the cardiac surgical patients, this group did not receive benzodiazepine (lorazepam) premedication and the patients were found to require a higher induction dose of alfentanil; incidence of

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TABLE

Opioid Administration Rate for Induction and Incremental Bolus Dose, Coronary Artery Surgery

	Rate of administration at induction (μg min^{-1})	Incremental bolus dose (μg)
Sufentanil	300	50
Fentanyl	400	250
Alfentanil	3000	2500

muscle rigidity was also increased (50%), but after muscle relaxants the anesthetic course was smooth (17).

Hemodynamic Stability. Sufentanil anesthesia provided greater cardiovascular stability during coronary artery surgery than did fentanyl used similarly and in equipotent dosage (16). The presence of chronic beta-adrenergic blocking therapy, specifically propranolol, significantly reduced the incidence of hypertensive episodes and the anesthetic dose requirements of sufentanil during coronary artery surgery (18).

Alfentanil administered intermittently in bolus doses did not confer any increased hemodynamic stability compared to fentanyl in patients undergoing coronary artery surgery (15). The incidence of transient systemic hypertension following severe surgical stimulation was higher with alfentanil than with fentanyl anesthesia (19). However, the faster onset of action of alfentanil quickly controlled these episodes; thus the stress response did not become established and the need for supplementary antihypertensive therapy was not increased. The short duration of action of alfentanil may have resulted in a transient inadequate concentration of the opioid at the receptor sites, resulting in these hypertensive episodes.

Although postoperative recovery was rapid after the alfentanil bolus technique (15), it was considered that a continuous infusion of alfentanil might enhance hemodynamic stability and facilitate anesthetic management.

Continuous Infusion of Alfentanil. No useful correlation was found between the total alfentanil dosage requirement and the age or weight of the patient (S. de Lange, unpublished data), as has recently been confirmed by other workers (20). In the absence of pharmacokinetic data, an infusion rate was calculated from the mean total dose of alfentanil given before, during, and after cardiopulmonary bypass in a previous study (15).

A variable-rate infusion of alfentanil 12.5–50 mg h^{-1} was compared to a bolus technique during coronary artery surgery (21). Bolus doses of alfentanil 2.5 mg were given or the infusion rate was adjusted according to the systolic arterial pressure response to anesthesia and surgery. Apart from the ease of anesthetic management, the infusion technique was superior to frequent boluses of alfentanil in maintaining hemodynamic stability and minimized the need for antihypertensive supplements (21).

Following the development of a radioimmunoassay technique for alfentanil (22), plasma concentrations during variable-rate infusion of alfentanil were measured and were related to clinical effect during coronary artery surgery (23). In this study, a mean infusion rate of 39 mg h^{-1} before bypass minimized the incidence of hypertensive episodes and resulted in a peak mean alfentanil concentration of 1.76 μg ml^{-1} at maximal sternal spread. The wide individual variation of plasma concentrations found necessary to block hypertensive responses to the same surgical stimulus, and the inability to find a useful correlation between the total dose of alfentanil required and the surface area, the patient's age, and the duration of the operation, make it difficult to formulate ideal infusion rates based on patient variables.

Cardiopulmonary bypass prolongs the terminal elimination half-life of alfentanil (S. de Lange, N. de Bruijn, unpublished data), as has been shown with fentanyl (24), and studies are now in progress in which postbypass pharmacokinetics are being measured and compared with results obtained in noncardiac patients. Variable-rate alfentanil infusions are also being adapted for general surgical cases, and preliminary results are encouraging.

Awareness and Recall. No episodes of awareness and recall have been recorded during these studies with alfentanil and sufentanil. Several precautions are taken to minimize such events:

1. Titration of opioid anesthetic induction dose to unconsciousness. This is a good indicator of further operative requirements. With alfentanil, a fairly good correlation was found between induction and total dose in μg/kg^{-1} (23).
2. Minimizing the use of long-acting muscle relaxants and delaying their use until at least 20 minutes after induction.
3. Continuous infusion of the opioids so that rapid falls in plasma concentration are less likely to occur.
4. Benzodiazepine—lorazepam, which has good antirecall properties (25)—in the premedication.

Suppression of Stress Hormone. Anesthesia with alfentanil and sufentanil prevents the rise of plasma levels of antidiuretic hormone and growth hormone during coronary artery surgery, including cardiopulmonary bypass (26). In this they are more successful than fentanyl, which does not block plasma antidiuretic hormone elevation during bypass (3). Plasma cortisol rise is also blocked throughout surgery, but plasma catecholamine levels rise during cardiopulmonary bypass (S. de Lange, T. H. Stanley, unpublished data); in this respect they resemble fentanyl anesthesia (27). Opioid anesthesia, especially with alfentanil and sufentanil, may interfere or block that region of the hypothalamus concerned with the regulation of stress hormone release from the anterior and posterior pituitary gland.

Summary

Both alfentanil and sufentanil are attractive alternatives to fentanyl for high-dose anesthesia techniques. They appear to compensate for some of the deficiencies encountered with fentanyl. Nevertheless, poorly administered high-dose techniques can give equally bad results whatever opioid is used. Sufentanil can provide very stable anesthesia, because it has greater access to and specificity for the opioid receptor sites than either alfentanil or fentanyl. Its high potency and long duration of action can easily result in overdosage, although side effects are minimal. Its long duration possibly limits its use as a high-dose anesthetic agent primarily to prolonged and major surgery. Alfentanil, because of its short duration of action and its rapid onset, is a very flexible agent. With variable-rate continuous infusion, high plasma concentrations can be maintained without unduly prolonging recovery, thus possibly advancing the concept of stress-free anesthesia.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Intravenous Anesthesia—History, Currency, Prospects

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Because I follow a long line of illustrious predecessors, I accept my role as principal lecturer to the 20th Bernard H. Eliasberg Memorial Symposium—with mixed feelings of humility, pleasure, and sobriety. My assignment is to examine the nature of intravenous anesthesia, currently and for the first time approaching equal status with the inhalation and regional methods—in the care of surgical patients. Since the symposium papers today have clearly depicted the present situation in the opinions of authorities the world over, I shall focus mainly on the origins of this approach to narcosis, for there the problems were envisioned and there the prospects for the future must lie. Incidentally, the history of intravenous anesthesia was exhaustively researched by R. Charles Adams of the Mayo Clinic, in his 1944 monograph on the subject.

When Bernard Eliasberg contemplated the practice of anesthesia in the second and third decades of this century, there was mainly history to rely on. The scientific basis of anesthesia was meagre indeed, as Henry K. Beecher discovered in 1938, when he could easily present all that was then known about the subject in a thin monograph of 388 pages entitled *The Physiology of Anesthesia* (1). Now, with astonishing developments in all branches of scientific medicine, anesthesiologists have a far better opportunity to establish intravenous anesthesia on a rational basis than was possible for the inhalation or regional anesthesia of Eliasberg's time.

History

As they are usually not trained historiographers, physicians who write history are prone to place undue emphasis on the importance of individuals or isolated events in rationalizing great discoveries, as was the approach in relation to the introduction of both general and regional anesthesia. Were I to follow this practice I could say that intravenous anesthesia began in the 1660s. Following William Harvey's studies on the circulation, Percival Christopher Wren felt the need to establish his priority over Daniel Johann Major (2), as the first to inject medicinals into the circulation. Thus in the *Philosophical Transactions* for 1665 (3), Wren wrote that he could "easily contrive a way to convey any liquid thing immediately into the mass of blood; thus, in pretty big and lean dogs by making ligatures on the veins and then opening them on the side of the ligature towards the heart; and by putting into them slender syringes or quills, fastened to bladders containing the matter to be injected." Upon encouragement from Mr. Robert Boyle, Wren proceeded with the experiments, "whereof the success was that the opium, being soon circulated into the brain did within a short time stupify, though not kill the dog; but a large dose of the crocus metallorum, made another dog vomit up life and all." The dried crocus or saffron was at the time employed as a stimulant, antispasmodic, and emmenagogue.

Wren and Major notwithstanding, the gastrointestinal tract remained the only route for medication until the late 1700s, when discoveries in pneumatic chemistry, respiration, and pneumatics culminated in the practice of pneumatic medicine at Bristol and Clifton, England. There, oxygen, nitrous oxide, and ether were inhaled for the relief of chest congestion and phlegm, and to treat pulmonary consumption, even to attempt cure of calculus and sea scurvy. Everyone knows of Humphry Davy's role in the discovery of anesthesia (4). After inhaling nitrous oxide, Davy, superintendent at Clifton, remarked: "As nitrous oxide in its extensive operation appears capable

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of destroying physical pain, it may probably be used with advantage during surgical operations in which no great effusion of blood takes place." Davy knew then what we have since rediscovered during anesthesia for cardiac surgery, that nitrous oxide stimulates the sympathetic nervous system under some circumstances.

Instrumentation. These precursors plus Henry Hill Hickman's subsequent employment of carbon dioxide for narcosis (5), and the popular ether and nitrous oxide frolics in England and America, led to the first public demonstration of ether anesthesia, in 1846. Wren thought of the intravenous route and observed the toxicology, but inhalation anesthesia had to arrive before intravenously induced narcosis might become a reality.

Around the early 1850s the hypodermic hollow needle and glass syringe were devised, again as in the introduction of anesthesia—via the multiple inventions of Francis Rynd (6), Alexander Wood (7), and Charles Gabriel Pravaz (8). Perhaps these devices presaged regional rather than intravenous anesthesia, as Rynd and Wood were making injections into the vicinity of nerves for the relief of neuralgia. Pravaz introduced ferric chloride into aneurysms, via trocar, in order to make them clot.

Thenceforth the development of intravenous anesthesia was simply a matter of the development of useful agents, their survival dependent upon appropriate pharmacodynamic and pharmacokinetic properties. One might transpose to the intravenous agents the comments of Samuel D. Gross relating to books and medical journals in 1876: "Some fall stillborn from the press, many die in their infancy, a few attain to a vigorous manhood and now and then one is fortunate enough to reach old age" (9).

Useful Agents: Morphine. As background to the later use of morphine in intravenous anesthesia: Sertürner, in 1806, purified morphine from opium and gave its chemical description in 1817 (10). Dissolved in water, morphine, taken for the relief of pain, caused redness of the face, dull headache, a tendency to vomit, and stupefaction resulting from the larger doses. These kinds of responses figure prominently in the choice of opioids for premedication today. No sooner had general anesthesia been introduced than morphine began to be used in conjunction with it. Walter Channing in his 1848 treatise *Etherization in Childbirth* (11) mentions the use of morphine for the mitigation of pain in the first stage. However, the redoubtable Claude Bernard arrived at a correct assessment of the use of morphine in conjunction with anesthesia, or mixed anesthesia as he termed it (12). In experiments done on dogs, "when one begins with chloroform followed by morphine on emergence," he stated, "the unconsciousness produced is long drawn out as a result of the influence of the morphine, but by giving the morphine first—scarcely is the inhalation of chloroform interrupted before sensibility returns. Thus one has a rapid means alternately to suspend or reestablish sensibility and this is important in certain cases." But Bernard did advise that morphine per se is not an anesthetic in the same sense that chloroform is. He noted that morphine decreases pain in the sensorium commune, directly or indirectly, and also stimulates sensory irritability.

Intravenous Route. W. Stanley Sykes, author of that splendid three-volume work, *On the First Hundred Years of Anaesthesia* (13), in an essay only recently published, cites Pierre Cyprien Oré as the true pioneer of intravenous anesthesia, one who employed chloral hydrate for that purpose. Oré's first report was addressed to the Surgical Society of Paris on May 29, 1872 (14). Utilizing a modification of the Pravaz syringe, because he found the latter was liable to transfix the vein and allowed the solution to be injected perivenously, Oré proclaimed that chloral was the most powerful of all anesthetics. As usual, opposition arose as the critics raised the possibility of the development of phlebitis and clotting in the veins. Oré subsequently published a monograph on the use of chloral hydrate intravenously with an account of 36 cases (15), some 15 for cataract extraction, others for treatment of tetanus. Oré claimed not to have encountered either clotting or thrombus in the veins, but there was one anesthetic death in a healthy middle-aged man undergoing cataract surgery. As the circulation and respiration were failing, one of the rheophores of an electric machine was applied to the epigastrium, the other over the course of the vagus and phrenic nerves. After initial slight improvement the patient died.

Anoci-Association Theory. Quite early in the 1900s an essential concept for the development of balanced anesthesia was advanced wherein intravenous anesthesia is the major component. In 1901, George W. Crile wrote a monograph on problems relating to surgical operations which provided the basis of his anoci-association theory (16). "In conscious individuals," he explained, "all noxious stimuli reach the brain. During general anesthesia only the traumatic stimuli are perceived centrally, while with complete anoci-association all stimuli are blocked." Then, in

1902, Harvey Cushing wrote (17) that circulatory shock during operation was the result of peripheral trauma to nerves with consequent depression of the central nervous system. Both men advocated the concomitant use of nerve block in the operative field just as Halsted before them had injected the brachial plexus during radical mastectomy. Both Crile and Cushing were intensely concerned with the anesthesia given their patients. Indeed, credit is given Cushing for coining the term regional anesthesia, in addition to his first use of anesthesia records, the measurement of blood pressure intraoperatively utilizing the Riva-Rocci technique and his advocacy of the precordial stethoscope.

The anoci-association theory was gradually accepted but was modified in the fifties to conform with new information on the endocrine response to stress involving the hypothalamic, anterior pituitary, adrenal cortical axis. The matter of stress figures large in modern concepts of anesthesia. Further, its neuroendocrine basis and inextricable relation to the sympathetic nervous system are major considerations in current intravenous opioid use for cardiac surgery. The work of the ischemic heart must not be augmented by increases in heart rate, contractility, or afterload and the myocardium must be specifically monitored so that the correct interventions can be made.

Quantification. In relation to autonomic responsiveness, Roizen and his confreres (18) just now have further refined the concept of minimal anesthetic concentration (MAC) in terms of MAC-BAR, the concentration of general anesthetic required to block the adrenal response to skin incision as manifested by pupillary dilation, increase in heart rate and blood pressure, and rising plasma norepinephrine concentrations. Except for the latter, these observations represent little more than the signs of anesthesia as first refined by Guedel and later modified in terms of reflex responsiveness by Gillespie. So many anesthesiologists these days claim that it is not possible to detect the signs and stages of anesthesia when modern anesthetic agents are employed, but this is not so. And I wish that an attempt had been made to establish some kind of MAC-BAR for the intravenous opioids in terms of their plasma concentration. Surely the time is ripe for a quantitative assessment rather than such imprecise terms as high-dose morphine or high-dose fentanyl. Roizen remarks that the adage "the less anesthetic the better" may be incorrect.

Other events basic to the development of intravenous anesthesia also took place at the turn of the century. In Crile's era the semisynthetic opioids—heroine and hydroxymorphine—began to be used. Likewise, in 1903, long after the synthesis in 1864 of barbituric acid or malonyl urea by von Baeyer (19), the first sedative barbiturate, diethyl barbituric acid, or barbital, a long-lasting hypnotic, was prepared by Fischer and von Mering; it was succeeded by phenobarbital or luminal. As the derivatives of barbituric acid are highly insoluble in water, the sodium salts were prepared for intramuscular and intravenous injection. Consequently, in 1921, Somnifene, a mixture of the diethyl amines of diethyl and diallyl barbituric acids, began to be used for intravenous sedation.

Early efforts to temper the use of inhalation anesthetics à la Claude Bernard arose when morphine and scopolamine in a dose ratio of 25:1 were used for premedication. Around 1905, Babcock proceeded to use these agents alone for a wide range of operations. While the patients seemed oblivious to pain, some required physical restraint, and the resultant high mortality led to abandonment of this regimen. Even the sage Ralph Waters dared give these drugs in repeated dosage as the only anesthetic agents for vaginal hysterectomy, claiming that the respiratory depressant actions of morphine were counteracted by scopolamine, which also provided psychic sedation. Major degrees of bradycardia and dryness of the mucous membranes also developed. One wonders why scopolamine isn't used more frequently today because of the salutary bradycardia and excellent psychic sedation, while reversal of its psychotomimetic properties can be accomplished with the antagonist, physostigmine.

Currency

Short-Acting Barbiturates. To be sure, the major impetus to the development of intravenous anesthesia was the advent of the short-acting barbiturates. Introduced by Bumm in 1927, Pernoston, in a 10% aqueous solution, was extensively used. Prior to this, intravenous alcohol and tribromethanol had been found wanting, and so had diethyl ether. Around 1928, John S. Lundy at the Mayo Clinic began to supplement inhalation anesthesia with amytal, then pentobarbital, intravenously. Both of these drugs had a relatively slow onset of action, according to modern standards. Hexobarbital, or Evipal, introduced in 1932 by Helmuth Weese, was the first rapidly acting intravenous anesthetic to achieve wide usage, even though anesthesia was accompanied by extraneous muscle movements. Eventually synthesis of the sulfur derivatives of barbituric acid provided the final touch, with the result that thiopental, a sulfur derivative of pentobarbital, was first used in this country by Lundy and by Waters. Dundee remarks (19) how interesting it is that this compound has withstood the challenge of so many others. Thus it appears that thiopental will not be easily replaced as an induction agent, while methohexital maintains a minor role as the briefest-acting agent of all.

The reasons for the survival of these drugs lie in their unique pharmacokinetic properties, first elucidated by Brodie and his colleagues (20) at New York University Medical School, a landmark in the study of all kinds of drugs in humans. After a single intravenous injection, the duration of action is brief because of ready transport to the brain in a high cerebral blood flow, rapid reversal of the initially high concentration gradient from the brain to venous outflow, redistribution via the circulation to the viscera with subsequent metabolism in the liver, or accumulation in adipose tissue, then slow release to plasma for final hepatic degradation. Despite this knowledge, many an anesthesiologist will induce inhalation anesthesia with a uniform "sleep dose" of thiopental ranging anywhere from 250 mg to 500 mg, so that the frequently resulting hypotension and respiratory depression interfere with the uptake and distribution of the inhalation agents breathed. Successive doses may be given to depress muscle movement caused by surgical stimulation during light anesthesia, even though the barbiturates are known antianalgesics, or they may be given to quell emergence excitement. Thus, during a preoperative visit, it is not surprising to hear from a patient, let us say a woman who had a dilation and curettage of the uterus, that she has an allergy to thiopental because she slept or had amnesia for 24 hours or more postoperatively.

Criteria for Balanced Anesthesia. In the forties, balanced anesthesia became the mode, that is, the use of sedatives and opioids for premedication, followed by thiopental for induction, then inhalation of cyclopropane or ether. Soon, tubocurarine began to be employed for muscle relaxation, thus obviating the need for the deeper planes of inhalation anesthesia. In 1954, David M. Little and Charles R. Stephen (21) defined criteria for balanced anesthesia—which might well be adopted by proponents of purely intravenous anesthesia—as follows: (a) hypnosis; (b) analgesia; (c) adequate oxygenation; (d) prevention of respiratory acidosis; (e) temperature control; (f) muscle relaxation; (g) obtundation of centrally mediated reflexes; (h) optimal working conditions for the surgeon; and (i) prompt return of physiological homeostasis postoperatively.

Analgesia. Although some might not view the research in this light, a major contribution to the understanding of intravenous anesthesia was the work of H. K. Beecher and his colleagues in the forties and fifties on the actions of opioids in relieving pathologic pain, that is, postoperative pain, rather than experimental studies in volunteers. A means of assessing analgesic effectiveness was established, in relation to a standard dose of morphine, 10 mg per kilogram body weight. When equianalgesic doses of the opioids are compared, little difference exists in the incidence of adverse effects. Thus, it is essential always to think in terms of equianalgesia when comparing the merits of different opioids. Beecher believed at the time that the opioids acted centrally, altering the usual alarm response to pain. In his studies of the injured at the Anzio beachhead, Beecher remarked on their seeming indifference to pain, which he attributed to a psychological adjustment to the possibility of their being removed from combat. Possibly he had an inkling, as some of his confreres suggest, of the existence of an endogenous hormonal substance which might account for the analgesia. Today we speculate on the multifold possible actions of the endorphins. Finally, in regard to Beecher, it was in his laboratory that the analgesic effects of the agonist-antagonist nalorphine were first investigated. As a result we now have a pure antagonist in the form of naloxone which figures so prominently in the reversal of opioids today, as well as the introduction of a new series of agonist-antagonists: butorphanol, nalbuphine, and buprenorphine, which thus far have not been extensively utilized in the regimen of intravenous anesthesia.

Neurolepsis. Around 1950, concurrent with the deliberate induction of body hypothermia as a means of protecting the brain during neurosurgery or cardiotomy, Laborit and Huguenard conceived the idea of artificial hibernation (22). An intravenous "cocktail" employed for this purpose consisted of L'Argactil or thorazine, one of the short-acting barbiturates, and the opioid meperidine. This combination, given intravenously in repeated dosage, resulted in a moderate degree of hypothermia, complete central nervous system dissociation, and, importantly, antagonism of circulatory shock. Although no firm data were supplied, they claimed that wounded French combatants in the Indonesian conflict suffered less from traumatic circulatory shock when given the cocktail. It was but a step further for DeCastro and Mundeleer (23) to create, in 1959, a similar condition of indifference, immobilization, and demineralization with the aid of a dissociative agent, the butyrophenone, haloperidol, and a new potent opioid, phenoperidine. Of interest is the knowledge that Oliver Wendell Holmes gave heed to the use of "neurolepsis" as a term to describe the phenomenon of etherization, rather than "anesthesia," which does not equate with the needs of modern practice. Neurolepsis, derived from the Greek, is a term found in the most venerable dictionaries, a state characterized by hypnosis and blockage of vegetative reflexes.

Just as the lives of the halogenated inhalation agents over the last 20 years have been short indeed, so have those of these newer intravenous substances. Haloperidol was replaced by droperidol (Inapsine), another butyrophenone, and phenoperidine was succeeded by fentanyl (Sublimaze). Now, even before its full potential may be realized or studies on its pharmacodynamics and kinetics completed, fentanyl is being supplanted by its congeners: alfentanil, sufentanil, carfentanil, and lofentanil. Janssen (24), in discussing these potent new analgesics, describes them as tailor-made for different purposes. What purposes other than analgesia, except for differing onset and duration of action? I continue to be puzzled as to why droperidol and fentanyl were initially prepared, then employed in a fixed combination as Innovar, when the requirements for either drug may vary so widely among individuals. Failure to realize the potential for harm of either drug in this mixture has led to serious morbidity and mortality in the hands of the unwary.

I reiterate that it is necessary to comprehend the pharmacokinetics and dynamics of these compounds, singly or in combination, in the practice of neurolept anesthesia. The emphasis now lies mainly on the intravenous opioids, a trend started by Lowenstein and his group in 1969 (25), when they began to employ a large-dosage morphine technique in cardiac surgery. I am not sure that there has been great improvement in this area over the initial use of morphine. Remember that Claude Bernard said that morphine alone was not an anesthetic.

Total Intravenous Anesthesia? A comprehensive outline of the current pharmacopoiea of intravenous anesthesia has been presented by the speakers in today's symposium. Some speak of total intravenous anesthesia, but this beclouds the fact that most of the regimen consists of induction agents, yet, in a broader sense, management of the airway and adequate alveolar ventilation will always be necessary. Furthermore, for operations in general, the neuromuscular blockers are often needed; the currently popular blockers themselves are in process of replacement. In the minds of many, inhalation of nitrous oxide analgesia is still a part of the intravenous approach. Despite the inroads of the halogenated agents, nitrous oxide remains the most widely used of the inhalants, the only survivor of the original ether, chloroform, and, later on, halothane. Humphry Davy was prophetic in stating that nitrous oxide might be used with advantage during surgical operations in which no great effusion of blood takes place. Moreover, in today's investigative climate, objections to nitrous oxide reside in the knowledge that nitrous oxide is a myocardial depressant per se, that it is toxic, possibly mutagenic and carcinogenic for operating room personnel when used in semiclosed rebreathing systems. Furthermore, a nonpharmacologic property of nitrous oxide as an inert gas, if indeed it is, is its tendency to diffuse into air-containing spaces in the body: middle ear, bowel, the tracheal cuff, air embolus in the circulation, and the air introduced for pneumoencephalographic studies. However, the greatest objection to nitrous oxide lies in its propensity for inducing hypoxia, responsible over the years for untold numbers of inadvertent hypoxic gas mixtures, leading to subtle degrees of cerebral hypoxia or cardiac arrest and permanent brain damage.

Prospects

Having spent most of my time on history—because it is that important—and more or less glossed over the present situation in critical manner, I now hesitantly assay to peer into the future. In doing so, I am aware, as one reviewer of a recent book on energy predictions recently remarked, that

> Nothing seems so dated as yesterday's version of the future. Optimism was as prevalent a generation ago as the gloom now sweeping the country. Economists then spoke complacently of fine-tuning the Keynesian Keyboard, and sociologists like Daniel Bell wrote of the end of ideology in a smooth postindustrial order. As for the developing world, it was on the take-off tarmac, in the confident view of Walt Rostow (26).

Should we be searching for the single intravenous agent that will supply all of the ingredients of anesthesia, as was once expected of the inhalation agents? I doubt the necessity or the prospect of success for this objective. However, few present here would dare say that any of the agents discussed in this symposium represent the ultimate.

The development of a new intravenous agent or agents probably depends upon parallel discoveries in neuropharmacology and neurophysiology, along the lines of central and peripheral neurotransmitters. Whereas at one point in history we believed that only two or three transmitters were concerned in neural transmission—epinephrine, norepinephrine, and acetylcholine—we now know of the presence of substance P, gamma-hydroxybutyric acid, dopamine, the endorphins and enkephalins, plus others active in neuroendocrinology; a total approaching 35, according to one observer.

We have come fairly close to a good agent among the diazepines and there are more of those on the planning board. With relatively few objectionable effects, these compounds are anxiolytics, active against insomnia and seizures—effective drugs against muscle spasticity, useful in preventing and treating local anesthetic seizures, and satisfactory amnesics with a dose-related duration of action. Moreover, to most everybody's surprise, biochemical and electrophysiological studies reveal that there are specific, membrane-binding sites for these zenobiotics that correlate specifically with their pharmacologic actions (27). Further, a benzodiazepine antagonist is now at hand (28). The receptors lie in close association with those responsible for the actions of gamma aminobutyric acid, while their actions may occur either at presynaptic or postsynaptic sites according to electrophysiological studies. Here the molecular actions seem to involve membrane channels, flow of chloride ions, and changes in conductance. I mention these developments not in any firm belief that a congener of diazepam will provide most of the attributes required for intravenous anesthesia. My purpose is simply to suggest again that an answer might be forthcoming in the realm of neuropharmacology and neurophysiology.

In conclusion, I would remind you that inhalation and regional anesthesia are still alive and well, with the same prospects for continued development as exist for intravenous anesthesia. The dictum had always been that inhalation anesthetics are almost completely recoverable so long as alveolar ventilation is maintained, but now we know that they, too, are metabolizable. When intravenous drugs are given, the body must dispose of them by processes beyond our control other than initial dosage.

I have on previous occasions of this kind given a quotation from Peter Caws' essay *The Structure of Discovery* which applies nicely both to the current and future status of intravenous anesthesia (29).

> Newton's celebrated remark about "standing on the shoulders of giants" reminds us that the development of science is a stepwise process; nobody starts from scratch and nobody gets very far ahead of the rest. At any point in history there is a range of possible discovery; the trailing edge of the range is defined by everything known at the time. (I overlook here the fact that people are constantly "discovering" what is already known, which blurs this edge somewhat), and the leading edge is a function of what is already known, together with variables representing available instrumentation, the capacity of human brains and so on.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Presentation of Eliasberg Medal to Professor Leroy D. Vandam

DAVID C. C. STARK, M.D.

It is my pleasurable duty to present the Eliasberg Medal to Professor Leroy Vandam. Dr. Eliasberg was one of the early educators in the Rovenstine mold, and it is most fitting that we are in a position to honor one of the great educators in our specialty in modern times.

Dr. Vandam was born in New York City, graduated M.D. from New York University in 1938, and prepared himself for a career in surgery by doing a year of pathology, a surgical internship, four years of surgery, and a year of surgical research, becoming chief surgical resident at Beth Israel Hospital in Boston. He interrupted his civilian career in 1943 to go into the armed forces, then returned to Johns Hopkins for two years of surgical fellowship with Drs. Alfred Blalock and Richard Bing. For reasons of health, on completion of this fellowship he moved to our side of the ether screen and commenced a residency in anesthesiology at the University of Pennsylvania. The decision to make this career change probably occurred at Hopkins under the tutelage of Austin Lamont, and he arrived at the University of Pennsylvania during the period of the most rapid development of its Anesthesia Department.

He always had a longing to return to Harvard, and Francis Moore, Moseley Professor of Surgery at the Peter Bent Brigham Hospital, found a willing candidate to be shanghaied to the Brigham in 1954. Dr. Vandam filled the directorship with the utmost distinction until his retirement some three years ago. Whatever biographical details culled from potted bibliographies may or may not tell one about a career, they tell little about the man. Vandam's forte has always been the education of the young. He is never happier than when surrounded by a group of medical students and interns—the medical school equivalent, I guess, of the "Pied Piper" situation. Committees and medical boards could await his arrival, but rounds, seminars, and student affairs inevitably took precedence.

His interest in writing, lecturing, and teaching is very evident from the well-known work, the bible by which we must all have lived: "Dripps, Eckenhoff, and Vandam"—what a triumvirate. He brings to his writing precision, economy of words, and clarity of thought, which are valuable staging posts in a career in anesthesiology. From 1962 to 1970 he was editor of *Anesthesiology,* and what a magnificant service he rendered. He deplores the exponential proliferation of solecisms, neologisms, malapropisms, split infinitives, hanging participles, and run-on sentences (such as this one) in many scientific journals. The editorial hatchets applied with such effect in the *New England Journal of Medicine* and *Anesthesiology* are due in large measure to his efforts.

It is not for me to suggest where his own greatest pride of achievement lies, but I would have to suspect that he is very proud of the Honorary Master of Arts that he received from Harvard, of his presidency of the Boston Medical Library, one of the largest collections of medical books extant in the world, and of anesthetizing the first patient to receive a successful renal transplant.

Not content with all these activities, somewhere in the early fifties he took up watercolor painting, and he is now justly famous for the quality and sensitivity of his New England seascapes.

"What do we have to do with time, but fill it with labor?" Vandam has certainly done just that. He is a most worthy recipient of the Twentieth Bernard H. Eliasberg Memorial Medal, whose inscription reads:

> Presented to Leroy D. Vandam, Professor of Anaesthesia Emeritus, Harvard Medical School, in recognition of his peerless contributions to Graduate and Undergraduate Medical Education and of the Scholarly and Cultural example he has set for his Profession and Specialty. December 4, 1982

From the Department of Anesthesiology, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY. Dr. Stark is now at Crouse-Irving Memorial Hospital and Upstate Medical Center, State University of New York, Syracuse, NY.

The Mount Sinai Journal of Medicine Awards 1982/83

Presented at Awards Ceremony June 3, 1983

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Journal Awards 1982/83

Student Prize

I Rand Rodgers, B.S., M.D.

The 1982/83 Student Prize has been awarded to I Rand Rodgers, B.S., M.D., for "Malignant Hyperthermia: A Review of the Literature" (vol. 50, no. 1, January/February 1983), and to Brian Baggott, M.D., for "Pheochromocytoma: A Clinical Study of the Role of Amines in the Development of Endocrine Dysfunction" (vol. 50, no. 3, May/June 1983). Each paper was written in the author's third year at Mount Sinai School of Medicine (CUNY). The Student Prize, established in 1971, is awarded to encourage students—the group from which future leaders of medicine may come—to explore the publication process.

The Globus–Mount Sinai Journal Award

Stanislaw J. Konturek, M.D.

Stanisław J. Konturek, M.D., is the recipient of the 1982/83 Globus–Mount Sinai Journal Award for his papers "Gastric Cytoprotection" and "Pharmacology and Clinical Use of Ranitidine" (vol. 49, no. 5, September/October 1982). Prof. Dr. Konturek is a senior member of the Institute of Physiology, Academy of Medicine, Krakow, Poland. The Globus Award is named for Joseph H. Globus, the founding and first Editor-in-Chief (1934–1952) of the JOURNAL. The award is for the best paper with a clinical orientation published during the academic year.

The Ralph Colp Award

Randolph M. Steinhagen, M.D.

Harvey J. Feld, M.D.

Randolph M. Steinhagen, M.D., and Harvey J. Feld, M.D., have received the 1982/83 Ralph Colp Award for their paper "Spontaneous Perforation of Intestinal Duplications" (vol. 49, no. 5, September/October 1982), written with Demetrius J. Pertsemlidis, M.D., who has declined to receive this award because of his senior status. Dr. Steinhagen has joined Mount Sinai School of Medicine academic staff and Dr. Feld plans to open a private practice this year. The Ralph Colp Award was established by colleagues and friends of Dr. Colp, distinguished surgeon and long-time Chief of Surgery of The Mount Sinai Hospital. Preference is given to, but is not restricted to, papers on surgical matters authored by junior members of the Department of Surgery.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Biopsy and Drainage of Intracerebral Lesions by CT-Guided Needle

MARTIN H. SAVITZ, M.D., S. SHELDON KATZ, M.D., JOHN P. JIMENEZ, M.D., AND HARVEY M. PECK, M.D.

Abstract

Eighty needle procedures monitored by serial computerized tomography were performed on 55 patients in two suburban hospitals. Under local anesthesia, 30 suspected brain tumors were biopsied, 17 intracerebral hematomas were evacuated, and 11 cerebral abscesses occurring in eight patients were drained. There were no complications of postoperative hemorrhage or infection. The simple and accurate methods presented have broad application in the practice of neurosurgery.

As soon as computerized tomography became widely available, needle biopsy of brain tumors assisted by CT scan was introduced at one university hospital (1). Drainage of intracerebral abscesses and hematomas under CT control was subsequently performed at other major medical centers (2–4). The original need for a water bag (1), the limited type of biopsy needles (5), the artifacts created by a metal needle (6), and the difficulty in using external landmarks without a stereotactic frame (7) were all problems discussed in the neurosurgical literature. The purpose of this paper is to report simple and accurate methods of biopsy and drainage which have been used at two suburban hospitals over a three-year period.

Method and Material

The patients were divided into three groups: 30 cases of suspected neoplasm, 17 cases of intracerebral hematoma, and 8 cases of brain abscess. Most of the abscesses and hematomas required more than one tap, but only 3 tumor patients underwent second biopsies. A preexisting postoperative cranial defect existed in 2 patients with brain abscesses and 1 with hematoma.

The initial diagnostic computerized tomography was reviewed, and the patient underwent a second limited study for the purpose of marking the scalp over the intracranial mass; additional intravenous contrast media was given when indicated. Indelible ink was used to record the thin red laser beam in plane with the scan that best visualized the lesion. The image containing the largest diameter of the mass was generally chosen. The trephine site was placed as close to the mass lesion as possible, but within the hairline, and avoided sensitive areas of the cortex.

In the operating room, the patient underwent a formal burr hole under local anesthesia. The dura was incised in a cruciate fashion after cauterization with a bipolar forceps. The small area of exposed arachnoid and cortex was also coagulated with a bipolar forceps and opened with a small scalpel. The skin was closed in two layers with fine sutures. The 1.5-cm trephine insertion site was planned exactly in the middle of the 3-cm incision.

A third series of CT scans was performed, either during the actual biopsy or during drainage of the intracerebral lesion. The relation of the burr hole to the mass lesion was visualized. The dimensions of the trephine site allowed for angulation of the needle when necessary. Correct positioning of the needle was accomplished on the first try approximately 80% of the time. Serial computerized tomography established the exact location of the needle tip, and a second pass was successful in the remaining cases. Closed skin held the needle steady during the procedure.

For biopsy of a suspected neoplasm (Fig. 1), the software component of the scanner measured the depth and angle of the tumor from the surface of

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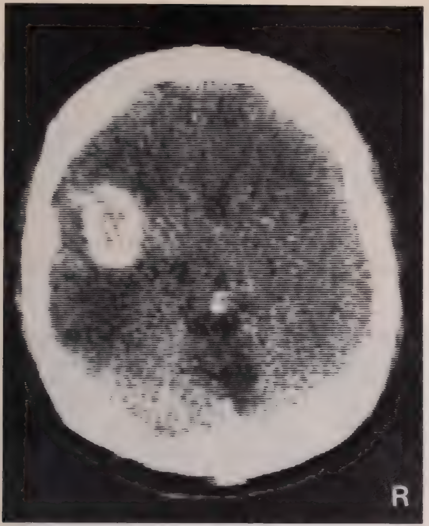

FIG. 1. Highly dense circumscribed lesion after intravenous injection of contrast media.

the scalp over the burr hole (Fig. 2). A 13-gauge Lee-Field needle, consisting of four coaxial components, was optimal. After the initial pass, the solid inner stylet was removed. The sharp tip of the outer cylinder provided a guillotine-like effect when the inner hollow cannula with a window was withdrawn. Any of the metallic components could be taken out during the procedure, allowing the plastic radiopaque sleeve to be used for viewing with little artifact (Fig. 3). The small amount of air which entered the needle provided accurate localization of the biopsy site. A frozen section was performed to confirm the histologic diagnosis of brain tumor.

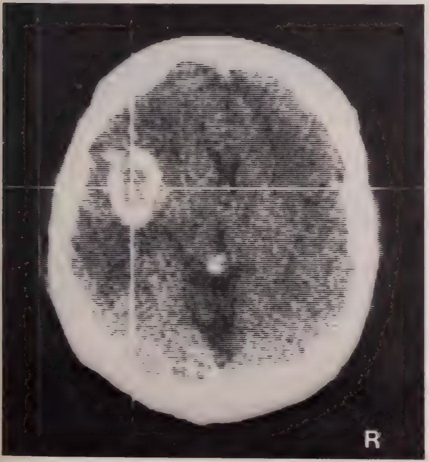

FIG. 2. Only the transverse measurement was available, but any angulation could be easily calculated.

Evacuation of an intracerebral hematoma (Fig. 4) was delayed at least 48 hours from onset to allow the clot to localize and partially liquefy. A 13-gauge, two-hole Cone ventricular needle with blunt end was employed in conjunction with a glass syringe for suction. Draining from opposite sides in the needle and at two separate depths minimized the need for repositioning to empty the collection of blood. The artifacts created by the stainless steel needle did not interfere with monitoring of drainage (Fig. 5). Removal of 30–50 cc of semisolid old blood was readily accomplished (Fig. 6).

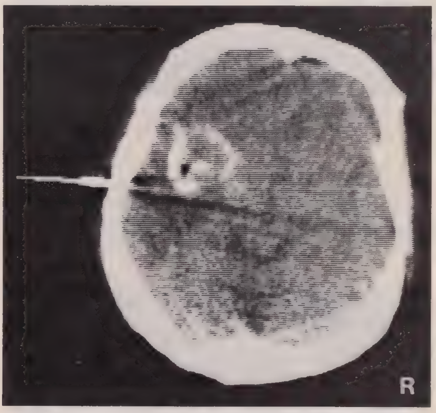

FIG. 3. Low-density air shadow within tumor identifies area of biopsy.

The capsule and cerebritis surrounding a brain abscess were best demonstrated by intravenous injection of contrast media for each of the CT procedures (Fig. 7). The same two-hole needle was used for drainage of purulent material (Fig. 8). An immediate Gram stain was performed, and aerobic and anaerobic cultures were begun. The amount of residual air or air-fluid level documented emptying and shrinkage of the abscess cavity (Fig. 9).

All of the patients received high-dose steroid therapy. Intraoperative prophylactic antibiotics

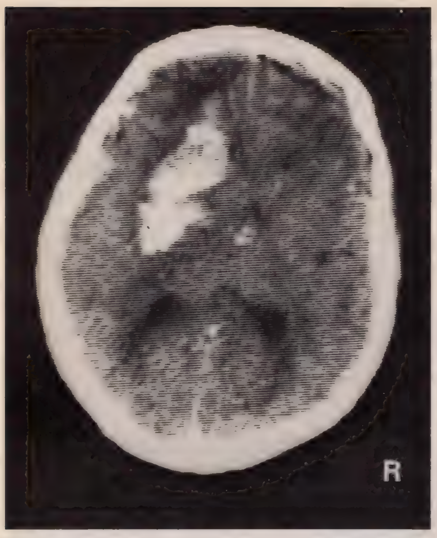

FIG. 4. Large irregular high-density area of hemorrhage in hypertensive patient; no contrast media was necessary.

were employed in the clean cases. A 1-gram intravenous dose of cefazolin was given as the incision was made in the operating room. Therapeutic doses of broad-spectrum antibiotics were begun as soon as the diagnosis of brain abscess was suggested on the first CT scan.

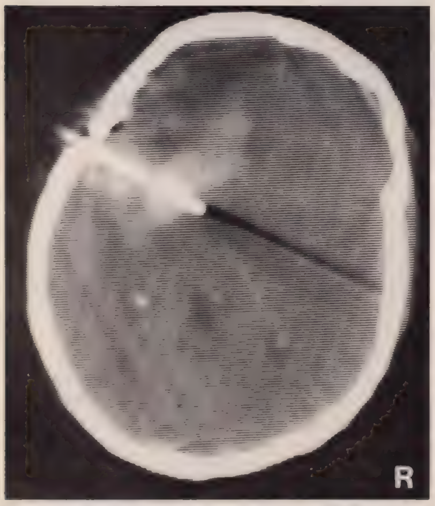

FIG. 5. Metallic artifact has been reduced by manipulating the window of the scanner.

Results

No wound infections occurred in any of the patients. Immediate and follow-up scans, taken after biopsy or drainage, failed to demonstrate any postoperative hemorrhage. There was no instance of increased neurologic deficit related to the needle procedures.

Of the 30 suspected brain tumors, 27 were diagnosed by needle biopsy—22 gliomas, 4 metastatic lesions, and one cerebral infarct. Early treatment with radiation and chemotherapy was instituted in the 26 cases of confirmed tumor. In 3 cases, the specimens were suggestive of neoplasm, but gliosis could not be ruled out; the patients underwent craniotomy and partial excision of low-grade astrocytomas.

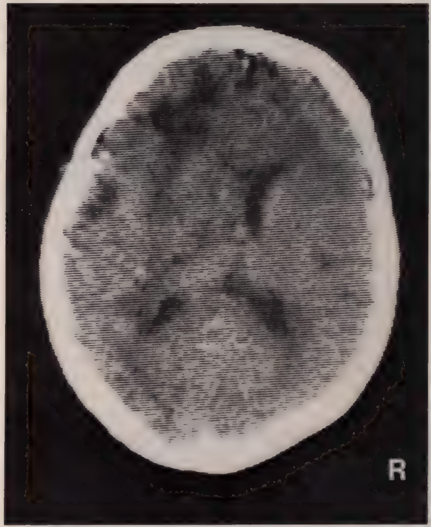

FIG. 6. Midline shift persists after drainage due to cerebral edema.

Seventeen cases of intracerebral hematoma required 31 drainage procedures. Fourteen of the 17 hemorrhages were secondary to hypertension, two resulted from rupture of an aneurysm, and one was due to cerebral vasculitis. Twelve patients improved after evacuation; five were unchanged.

All of the brain abcesses resolved after drainage. Six large lesions were drained twice, and a solitary lesion required only one drainage. One patient developed multiple small areas of intracerebral purulence after undergoing extensive craniectomy for subdural empyema and infectious sinusitis; each of 4 separate abscesses was drained once and did not recur. The cultured organisms varied, but six of the pathogens were anaerobic.

Discussion

The morbidity and mortality of the methods described are projected to be quite low with local anesthesia and careful preparation of the access site. Seeding of a brain tumor or an abscess along the needle tract has not occurred. No postoperative hemorrhages were observed in our series of 80 needle procedures, but this complication has been reported (2, 5). Steroid therapy reduces the chance of neurologic deterioration following manipulation of the edematous brain. Special positioning of the head was not required in any of the cases reported here. Exact anatomic localization of an intracranial mass by computerized tomography would seem to obviate the necessity of more elaborate stereotactic equipment. The use of CT control to direct the placement of needles for biopsy and drainage of intracerebral lesions has broad application in the practice of neurosurgery.

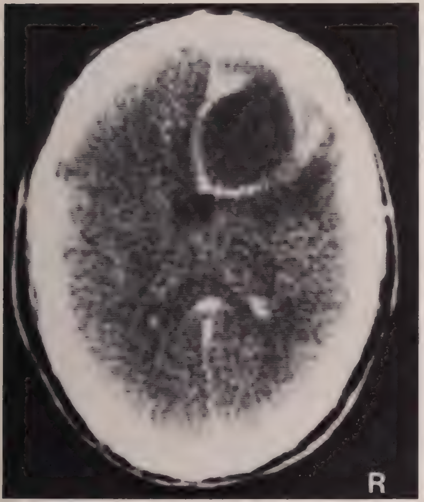

FIG. 7. Right frontal abscess 50 cc in volume, outlined by enchancing rim.

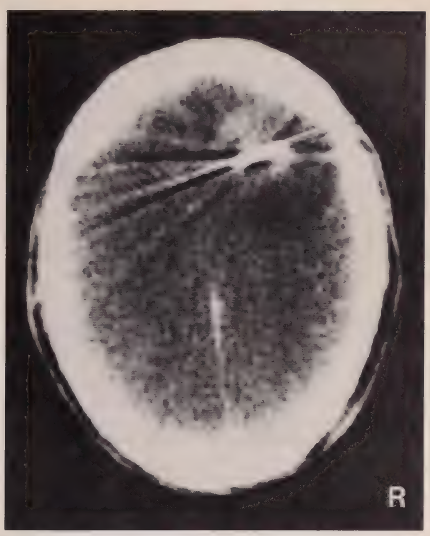

FIG. 8. Needle artifact does not interfere with localization of tip.

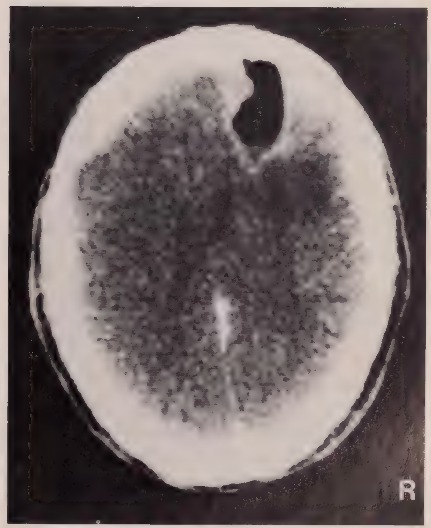

FIG. 9. Diminished size of cavity is evidenced by air shadow.

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Submitted for publication April 1983.

The Mount Sinai Journal of Medicine
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Stress and Diseases of the Upper Gut: II. Stress and Pancreatic Disease

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Abstract

Acute pancreatitis following various forms of medical or emotional stress (surgery, trauma, drugs, infections) presents histopathologic changes which can be attributed to neurohumoral and vascular effects. Animal experiments and the occurrence of similar lesions following shock and other low-flow syndromes suggest that the common denominator of stress is the pathogenic mechanism of hypoperfusion, ischemia, and parenchymal hypoxia. These findings reinforce blood-volume restoration and pancreatic perfusion as crucial in therapy and suggest that steroids have therapeutic value in the handling of the stabilization of epithelial membranes.

Stress and stomach ulcers were first paired in the days of the Roman Empire (1). Through the centuries, from John Hunter in 1772 (2) to Dieulafoy in 1910 (3), mucosal necrosis and inflammation of the gastrointestinal tract following pneumonia, strangulated hernia, and appendicitis have been cited (4). Only in recent years has stress been linked with pancreatitis in the literature (5–8).

Gallbladder disease and alcoholism are generally accepted as the principal etiological factors in pancreatitis. In some reviews a third factor, idiopathic stress, is noted, and as awareness of stress as causative has grown, it has been refined into more discrete factors (for example: postsurgery, trauma, thermal extremes, infections, shock, hemorrhage, drugs, metabolism, specific medical illness).

The hypothesis that pancreatitis could be a disease of adaptation was explored in 1956 (6). The purpose here is to reinforce this relationship: namely, that there is a common denominator among the etiological factors. As stressors, they all cause a neurohumoral and vascular response that produces similar pathological changes in the pancreas.

Postsurgical Effects. Pancreatitis following surgery in the upper abdomen, that is, the gallbladder, stomach, pancreas, and spleen (9–11), and possibly pancreatitis following renal allografts (12) may be due to faulty technique or trauma to the gland. However, postoperative pancreatitis following nonabdominal surgery (13, 14), including transurethral prostatectomy (15), cannot be explained on this basis.

Trauma. Trauma to the upper abdomen may cause direct injury to the pancreas and result in acute disease (16). But this line of reasoning cannot explain the reported cases of pancreatitis following nonabdominal wounds, such as crush injuries and fractures (17).

Thermal Extremes. Pancreatitis following hypothermia (18, 19) and burns (13) has been reported, but no satisfactory explanation has been offered.

Infection. Infection, either local or systemic, is not infrequently mentioned in the etiology of acute pancreatitis. Pancreatitis that follows penetrating ulcers of the stomach, duodenum, or colon may have a basis in infection. Systemic viral infections (20), as in mumps (21), chicken pox, and Reye's syndrome (22), find few supporters who involve the virus as a direct causative agent. Generalized sepsis, even following typhoid fever (23), seldom yields positive cultures from the pancreas, and in the rare cases of positive findings, there is great doubt of the significance of these findings.

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Drugs. In the past decade, much attention has been given to the role of drugs as a causative agent (24); well over twenty drugs have been discussed in this connection. Thiazides have been incriminated by producing necrotizing vasculitis (25). There are no conclusive answers on the pancreatitis-related effects of the many other drugs suggested as causative agents. Sherlock, writing on drugs and the liver, has stated that "drugs seem rarely to cause damage by a direct action on the liver cell" (26). One might anticipate, with the lack of evidence to the contrary, that drugs are not likely to cause damage by direct action on the pancreatic cells.

Shock. Shock from whatever cause, whether cardiogenic, anesthetic, septic, or hemorrhagic, increases the susceptibility of the pancreas to destruction, according to Warshaw and O'Hara (27). Hypotension produces ischemia, which results in tissue hypoperfusion. Indeed, experimental evidence indicates that pancreatic blood flow is markedly reduced in acute pancreatitis in the absence of shock (28). Ischemia, not hyperemia, is the basic pathophysiology of acute pancreatitis, according to Donaldson et al (29). A parallel can be drawn from the work of Ellenberg and Osserman, who initially emphasized the role of shock in the production of centrolobular necrosis of the liver, but finally concluded that this pathology is not specific for shock, but is probably the end result of vasospasm, anoxia, and acute circulatory insufficiency (30).

Medical Conditions. The appearance of acute pancreatitis following certain medical conditions such as myocardial infarction (31, 32) remains unexplained. Those conditions associated with systemic vascular effects, such as lupus erythematosis and periarteritis nodosa, can be accounted for on the basis of circulatory embarrassment to the gland. In the reported cases complicating a cerebrovascular accident (31) one is left with only hypothetical answers. That the nervous system plays a role in the production of acute pancreatitis was demonstrated experimentally by Mallet-Guy in guinea pigs and dogs after the stimulation of the left splanchnic nerve (33). Gilsdorf et al enhanced the development of hemorrhagic or lethal necrotizing pancreatitis from a mild or nonlethal bile-induced form by the excitation and overactivity of the sympathetic nervous system (34).

Among the many other causes of pancreatitis cited in the literature are oral contraceptives (35), pregnancy (36) and postpartum conditions (37), scorpion stings (38), vitamin-D poisoning (39), diets deficient in fatty acids (40), air pollution (41), hypercalcemia of multiple myeloma (42), and iatrogenic hypercalcemia from hyperalimentation (43).

Emotional Stress. In 1956, the thought that the same emotional stress responsible for gastric lesions (44) could precipitate pancreatic ischemic changes (6) was presented. Experimentally, one case of acute hemorrhagic pancreatitis was incidently observed during the production of gastrointestinal lesions in behaviorally conditioned monkeys (45). Gambill noted that some patients, when unusually tired or under great stress, not uncommonly developed painful attacks of relapsing pancreatitis (46). Warwick and Leavitt specifically relate a case of a six-year-old child with relapsing pancreatitis who experienced recurrent episodes as a result of severe emotional difficulties between her parents (47). M. R. Porter, associate professor of clinical surgery at the College of Physicians and Surgeons at Columbia, when questioned regarding the etiologic factors in acute pancreatitis, is quoted as responding, "We feel sure psychic factors do play a role in pancreatitis. We have one patient who gets acute pancreatitis every time she argues or fights with her husband. It can be predicted that when she has a quarrel, she will then come in with a pain in her abdomen half an hour or an hour later. We will find the amylase high and symptoms of pancreatitis" (48). The sixteenth-century British physician J. Aubert reportedly noted: "*Highmore corp. human Anatom. lib.* I, *part* II writes that he once observed in a Noble woman who for some years was perplexed with Convulsions, Epilepsy, and Hysterick passion, these having made her yield to Death; her dead Body being opened, the Pancreas was wholly found ill-affected and ulcerated" (49).

Some years ago, a number of pathologists were sent a questionaire asking, "Can the etiology of acute pancreatitis be ascertained by the gross or microscopic examination of the pathological specimen?" The answer was invariably "No." The similarity in pathology, in our opinion, suggested a single pathogenesis.

Experimental Findings. Goodhead in 1969 experimentally investigated the hypothesis that during the acute phase of acute pancreatitis, a decrease in blood flow in the microcirculation was the significant factor which resulted in the development of pancreatic necrosis (50). The perfusion rate was 23% of normal, causing tissue anoxia and acidosis. Donaldson et al in 1978 reported a 72% reduction in pancreatic arterial blood flow within three hours after induction of pancreatitis (51), and a 60% reduction in oxygen consumption within two hours.

Pancreatitis is usually produced in dogs by the injection of trypsin, bile, or blood, or a combination of the three, into the main pancreatic duct. Anderson suggested that a specific vasotoxic substance was formed in the gland which damaged the endothelial lining of the blood vessel, resulting in thrombosis and the development of hemorrhagic pancreatitis (52). However, this so-called vasotoxic effect is not localized to the pancreas, but apparently is a systemic effect in that the blood pressure and cardiac output are significantly decreased (50, 51) and the blood flow to the other viscera, duodenum, jejunum, ileum, and colon, is also measurably reduced (28).

Kaplan and Wheeler (53) concluded that all stress-related etiological factors produced a similar microscopic picture in the liver, namely centrolobular necrosis or degeneration. This was attributed to vasospasm, ischemia, and hypoxemia. Thus, it appears that since the pathologist is unable to differentiate pancreatitis, diseases of the pancreas, like those of the liver and the gut, result from the neurohumoral and vascular effects of various stressors. It follows that the primary effects are ischemia, hypovolemia, and anoxia or hypoxia, which result in the destruction of the cells of the gland.

Acknowledgments

The authors are very grateful to the librarian of the Touro Infirmary, Patricia J. Greenfield, and her assistant, Mary E. Hess.

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Submitted for publication November 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Studies in Pancreatic Secretion: VIII. Pancreatic Function in Patients With Wilson's Disease

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Wilson's disease (hepatolenticular degeneration) (1) is an inherited metabolic disorder in which a defect in ceruloplasmin is associated with widespread deposition of copper within the tissues of various organs (2). There ensues cellular disruption, which results in severe dysfunction of the central nervous system (1), the liver (3, 4), and the kidney (5). The possibility of pancreatic involvement has been considered by some investigators (6, 7), suggested by (a) the pancreatic dysfunction observed in hemachromatosis (8), in which the iron deposition in the gland results in cirrhosis, (b) the therapeutic use in Wilson's disease of penicillamine, a drug inducing pancreatic inflammation, lipomatosis, and dysfunction in animals (9, 10). Lankisch et al (7) found the pancreatic secretion in 5 out of 5 patients with Wilson's disease to be normal; Oswald et al (6) reported 3 of 3 patients with Wilson's disease to have deficient pancreatic secretion. Both used the secretin-pancreozymin test. The present investigation attempts, by study of a larger series, to resolve the reported discrepancies and to inquire, as well, concerning the role of penicillamine medication in the reported pancreatic deficiency states.

Methods

Ten patients were studied. Three patients were referred to the Pancreatic Research Laboratory during workup for digestive complaints and were later diagnosed as having Wilson's disease; these patients had not received penicillamine. Seven patients were referred to the Laboratory by Dr. Irmin Sternlieb. Six of these patients had been receiving penicillamine. Dr. Sternlieb made the assessment of clinical severity of the disease in these 7 patients, and also furnished other data. Informed consent was obtained from these patients.

All patients were studied by standard secretin test technique using a 1 unit/kg bolus of secretin and a collection period of 80 minutes. The four secretory parameters determined were rate of flow; maximum bicarbonate concentration; rate of enzyme secretion (amylase); and icterus index of the divided specimens (10, 10, 10, 10, 20, 20 = 80 min).

The first three parameters determine pancreatic function and were interpreted according to recognized patterns of secretion (8): (a) total deficiency, all parameters decreased; (b) qualitative deficiency, decreased maximum bicarbonate concentration; (c) quantitative deficiency, decreased flow; (d) isolated enzyme deficiency, diminished enzyme secretion; (e) hypersecretion, increased flow.

The fourth parameter defines the patency, capacity, and function of the extrahepatic biliary tract (12) in terms of the absence, disappearance, or persistence of bile pigment during the periods of active pancreatic secretion.

Results

The pancreatic and biliary responses to standard secretion stimulation in ten patients with Wilson's disease is presented in Table I. All patients displayed abnormal pancreatic secretion.

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These studies were supported by an Alfred and Florence Gross Research Grant.

TABLE I

Population Characteristics and Secretin Test Data, Wilson's Disease Patients

Patient No.	Sex	Age	Penicillamine	Secretin Test Volume ml/kg/80′	Maximum HCO_3 mEq/L	Amylase Secretion μ/kg/80′	Biliary Response
1	M	12	0	3.1	*76*	*5.0*	N̸
2	M	18	0	*8.4*	95	8.2	N
3	F	14	0	*0.5*	*49*	*2.5*	N̸
4	F	22	+	2.5	102	*2.5*	N
5	M	29	+	2.9	*73*	*5.5*	N
6	M	17	0	*12.1*	*42*	14.5	N̸
7	F	18	+	*0.3*	*42*	*1.4*	N̸
8	F	16	+	2.3	*86*	*5.8*	N̸
9	F	27	+	*4.7*	90	16.4	N
10	M	28	+	2.7	*75*	13.2	N
Normal Range				2–4	90–130	6–18	

The pattern of secretion varied:

Total secretory deficiency—patients 3 and 7.
Qualitative secretory deficiency—patients 1, 5, 8, 10.
Isolated enzyme deficiency—patient 4.
Hypersecretion—patients 2, 6, 9.

Abnormal pancreatic function was encountered in patients receiving penicillamine (patients 4, 5, 7, 8, 9, 10) as well as those who had not received this drug.

The biliary flow was abnormal in half of the patients. Abnormal biliary pigment response to secretin could not be correlated with a specific pattern of pancreatic secretion.

Discussion

Consistent abnormality of pancreatic function in this series of patients with Wilson's disease is in accord with the report of Osswald et al (6) but in sharp disagreement with the observations of Lankisch et al (7). The difference in finding of the latter investigators could derive either from a difference in technique in assessing pancreatic function or from a difference in interpretation of data. In 1971 (Lankisch), no attention was paid to secretory responses greater than the upper limit of the normal range, that is, hypersecretion as an indication of minimal to moderate pancreatic secretion had not been reported and accepted as a diagnostic pattern (13).

The variety of patterns of secretory abnormalities observed is unexpected and suggests a wide range of pancreatic pathology, from minimal inflammation to advanced and severe disease. Yet these laboratory findings could be correlated neither with the severity of the primary disease nor with complaints of abnormal bowel function such as diarrhea, steatorrhea, or evidence of intestinal malabsorption.

The abnormality in biliary flow in response to secretin observed in half of the patients is consistent with the "cirrhosis" which is part of the disorder. However, again, there was no correlation between abnormal biliary flow and clinical severity.

While the findings indicate that Wilson's disease, per se, is associated with pancreatic functional derangement in that abnormal secretion was observed in patients who had not received penicillamine, the study does not exclude the possibility that the drug does contribute to pancreatic involvement in those patients treated with penicillamine.

The investigation has answered the question of pancreatic participation in Wilson's disease but poses the following questions to be resolved.

1. Why do most patients with Wilson's disease fail to complain of diarrhea, steatorrhea, or malabsorption?
2. Given the pancreatic secretory defects observed, would these patients benefit from oral enzyme supplements?

Summary

Abnormal pancreatic secretion was encountered in all ten patients with Wilson's disease.

Abnormal biliary flows were observed in 50% of these patients.

The secretory defects could not be correlated with (a) clinical severity of disease, (b) gastrointestinal complaint, or (c) previous administration of penicillamine.

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Submitted for publication April 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Effect of Caloric Restriction on Neoplasm Growth

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Abstract

The effects of balanced caloric restriction on the growth of tumor were investigated. In the first of two experiments, 97 adult Paris mice were calorie restricted to 50%–62.5% of control levels and stabilized at a lower body weight; 100 were allowed to eat ad libitum prior to inoculation with Rauscher leukemia virus. In experiment 2, 80 mice were calorie restricted to 75% of control levels. Mice fed calorically restricted diets demonstrated significantly smaller spleens than their well-fed counterparts, although some splenomegaly was noted in all inoculated mice. Microscopically, the spleen and liver of diet-restricted inoculated animals showed absence of malignant cells with preserved tissue architecture or less malignant changes compared to controls. Results suggest that balanced caloric restriction slows and may prevent infiltration by Rauscher leukemia virus. Because gross and microscopic findings do not coincide, conclusions as to the protectiveness of underfeeding against establishment of malignant viral cells cannot be drawn.

The effects of protein-calorie malnutrition on the susceptibility to and growth of neoplasms in laboratory animals have been well documented (1–4). In contrast, there have been few studies of balanced caloric restriction and the incidence and rate of growth of tumors (2). We subjected laboratory mice to a period of balanced diet restriction, inoculated them with a leukemia virus, and studied the effect of the diet on tumor development.

Materials and Methods

Experiment #1. Adult Paris mice were obtained from colonies bred at the Institute for Cancer Research of the College of Physicians and Surgeons of Columbia University, in New York City. The mice were originally kept in groups of ten per cage and segregated by sex, but calorie-restricted mice were later placed in individual cages to prevent cannibalism. Mice maintained on normal diet were not caged separately. A commercially available laboratory chow for mice (Purina Co., St. Louis, MO) was fed to all mice. The chow contains approximately 23.0% protein and 4.5% fat, supplemented with vitamins and minerals.

Ninety-seven mice (48 females, 49 males) were begun on diets restricted in calories by 50%. Restriction was achieved by providing a measured weight of chow equal to 50% of that eaten by controls. After 10 days of this diet regimen, the weight of food supplied was increased by 25%, increasing total calorie intake to 62.5% of control values; this level was maintained for the remainder of the study. The remaining 100 mice served as controls and were supplied with chow ad libitum. In an attempt to compensate for the excessive mortality thought to have resulted from over-restriction of food intake, 20 control mice (10 females and 10 males) were fed diets that were 62.5% of control levels, beginning two weeks after the start of dietary manipulation. All animals had free access to water throughout the experiment. Animals were weighed individually, using a Mettler balance, every fifth day.

Experiment #2. A second group of mice (41 females and 39 males) was caged separately, before dietary restriction was imposed. Again, non-diet-restricted mice were segregated only by sex. The same commercial chow was provided. The experimental diet supplied 75%, by weight, of normal

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intake. Food was rationed daily and water was continuously available. Controls were given chow ad libitum. Each mouse was weighed at five-day intervals.

Inoculation and Endpoint. The Rauscher leukemia virus (5) was selected for this study. Rauscher leukemia virus is a murine-derived, RNA tumor virus system, which causes lymphocytic leukemia and death in host animals. Positive viral takes can be expected in 90%–100% of the experimental population. A Balb-C mouse plasma citrate, 1:1 dilution (University Laboratories Corp., Highland Park, NJ), was injected intraperitoneally into 10 mice to develop a species-specific strain. After a 16-day establishment period, mice were sacrificed and spleens removed. The spleens were homogenized in a Parker homogenator with Dulbecco's PBS (10 ×) buffer (calcium and magnesium free) (1). The homogenate was centrifuged at 10K rpm for 15 minutes. The supernatant was used as inoculum.

After approximately 2 weeks of dietary stabilization, 28 (14 females and 14 males) calorically restricted mice and 20 (10 females and 10 males) control mice were injected intraperitoneally with approximately 2×10^4 viral particles. Mice were sacrificed serially at 2, 5, and 7 weeks after inoculation with Rauscher leukemia virus. Each mouse was dissected, viscera examined macroscopically, and spleens removed and weighed. In addition, representative spleens and livers were selected from one or more animals in each group for histological study and were fixed in 4% buffered formalin and embedded in paraffin, and sections stained with hematoxylin-eosin.

Results

Body Weights. Mice fed calorically deficient diets weighed less than those animals on control diets. The greater the degree of caloric restriction, the greater the weight loss. In all diet groups, weights had stabilized prior to inoculation with Rauscher leukemia virus.

Mortality. Of the calorically restricted mice in experiment 1, 77% died prior to the end of the study; most of these died prior to inoculation, but 14% of the deaths occurred after injection with Rauscher leukemia virus. The average spleen weight of these mice was 282.8 mg. Only one inoculated control mouse died prior to the end of the experiment, two weeks after inoculation; the spleen weight was 1880 mg. All noninjected controls survived.

In experiment 2, 35% of the diet-restricted mice died before sacrificing, including one mouse (4%) in the calorically restricted inoculated group. The spleen of that mouse was 71.0 mg. None of the ad libitum, inoculated mice died prior to sacrificing.

TABLE I

Relative Spleen Weights

Time	Specimen	Corrected Weight (mg/100g)
Experiment 1		
5 weeks	noninjected, 62.5% diet	283.7
	injected, 62.5% diet	3042.2
	noninjected, control diet	605.0
	injected, control diet	4406.8
7 weeks	noninjected, 62.5% diet	636.1
	injected, 62.5% diet	3110.0
	noninjected, control diet	633.5
	injected, control diet	3674.7
Experiment 2		
2 weeks	noninjected, 75% diet	473.8
	injected, 75% diet	836.9
	noninjected, control diet	666.3
	injected, control diet	2254.9

Splenomegaly. The calorically restricted mice in experiment 1 had significantly smaller spleens than their well-fed counterparts ($p < 0.05$) after 5 and 7 weeks. A significant difference is present whether we consider animals surviving to the end of the experimental period or those dying prior to the time of sacrificing.

In experiment 2, reduction of caloric intake by

TABLE II

Degree of Infiltration by Tumor Cells

Specimen	Infiltration Spleen	Infiltration Liver
ad lib. diet, noninjected	–	–
Experiment 1		
noninjected, 62.5% diet*	–	–
injected, 62.5% diet	+ +	+
injected, control diet*	+ + +	+ + +
Experiment 2		
noninjected, 75% diet*	–	–
injected, 75% diet	–	–
injected, control diet*	+ +	+ +

Key
– No evidence of infiltration by malignant cells Tissue architecture intact. (Fig. 1A)
+ Evidence of slight infiltration by malignant cells Tissue architecture intact. (Fig 1B)
+ + Moderate infiltration by malignant cells Evidence of some tissue destruction. (Fig 1C)
+ + + Extensive infiltration by malignant cells Tissue architecture completely disrupted. (Fig 1D)

* Specimen found to be infected with parasites on histologic examination; source unknown.

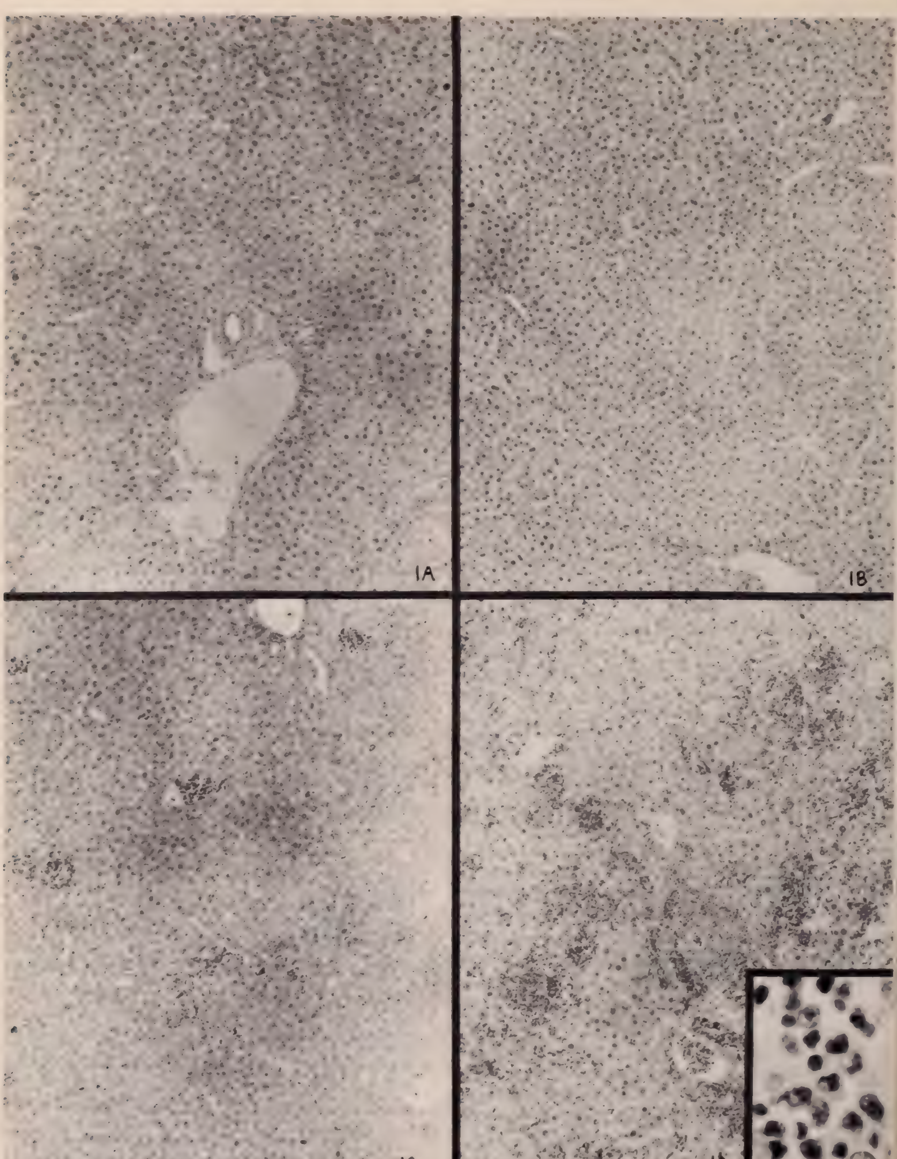

FIG. 1A. Photomicrograph, liver without infiltration of tumor cells, from noninjected animal on normal diet (hematoxylin & eosin, ×200).

FIG. 1B. Photomicrograph, liver with mild (+) infiltration from injected animal on 62.5% diet (×100).

FIG. 1C. Liver with moderate (+ +) infiltration from injected animal on normal diet (×40).

FIG. 1D. Liver with marked (+ + +) infiltration from injected animal on control diet (×40). Inset: infiltrating lymphocytic cells (×400).

25% was also sufficient to significantly retard spleen enlargement ($p < 0.05$) as compared to controls.

Even after correction for total body weight (Table I), morphologic evidence of leukemia cell proliferation was less marked in calorically underfed animals than in their ad libitum counterparts.

Histology. The histologic findings are summarized in Table II. The degree of infiltration was estimated in terms of the number of leukemia cells present as well as the extent of replacement of normal architecture. Infiltration by leukemia cells was less marked in those animals most severely restricted in caloric intake, whereas only those animals receiving control diets had intense infiltration (Figure 1).

Discussion

It is a common belief that poor nutrition predisposes to infection. Recently, however, it has been suggested that the infectivity of microorganisms decreases with reduction in the quality of nutrition and that immunity is enhanced (6). Caloric underfeeding inhibits the development of mammary adenocarcinoma in mice (2). Chronic caloric restriction has also been shown to reduce the incidence of spontaneous tumors in laboratory rodents (7). In contrast, isocaloric, low-protein diets are associated with decreased morbidity from malignant lymphomas (8).

Our experiments were undertaken to determine the effects of chronic, balanced malnutrition on the growth of neoplasm. Weight reduction was easily achieved; animals lost as much as 10%–20% of body weight in a five-day period. However, the mortality was high. This was thought to be due to the severe calorie restriction imposed and rations were increased. In spite of this, mortality persisted, but at a somewhat lower incidence. A second group of mice was fed 75% of the caloric level of control animals in an attempt to achieve a stable, viable model of malnutrition. Mortality rates were lower, but the population could not be considered completely stable, and animals continued to die, apparently as a result of malnutrition. The average spleen weights of mice dying after inoculation, but prior to the planned time of sacrifice, in the calorically restricted diet groups were 282.8 mg (experiment 1) and 71.0 mg (experiment 2).

Spleen enlargement was present in all injected animals. Calorie-restricted mice had less splenic enlargement than their well-fed counterparts. Malnutrition does not prevent all manifestations of malignant disease, but does have a retardant effect upon tumor growth. Five of the ad libitum, Rauscher leukemia virus inoculated mice had spleens weighing more than two grams. The greatest spleen weight in a calorically restricted mouse was 1.1 gm. When spleen weight is corrected for total body weight, the results are less impressive, but still obvious. Absolute spleen weight correlates well with the histologic findings and is probably a more accurate indication of infiltration.

Histologic examination provided evidence that malnutrition may retard leukemia cell proliferation. Infiltration was less marked, after seven weeks, in calorie-restricted inoculated animals. The inoculated group on the 75% diet showed no evidence of leukemia two weeks after inoculation with Rauscher leukemia virus. In contrast, infiltration was present in the injected group on an ad libitum diet after two weeks.

A parasite was found in many of the animals (Table II). Although this may have contributed to the death of some animals, its distribution in all experimental groups suggests that the presence of the parasite does not alter our results.

It would appear that establishment of the tumor cells may be delayed by underfeeding, and that continued growth and proliferation of the tumor cells is slowed (Table II). It is tempting to speculate about the role of weight loss in humans with cancer. Is weight loss an attempt by the host to slow tumor growth? Is caloric restriction of value in reducing tumor burden and, consequently, of possible value in enhancing the success of adjuvant therapy? Is there a level of diet restriction that provides minimal deleterious effect on the host and maximum tumor growth inhibition? Additional research is needed to clarify the role and mechanism of caloric restriction in animals with tumors.

Acknowledgments

The authors thank the late Dr. S. Speigelman, Director, Cancer Center/Institute of Cancer Research, Columbia University, for his advice and the use of his facilities and Stephen A. Geller, M.D., Professor of Clinical Pathology, Mount Sinai School of Medicine, for his suggestions and support.

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Submitted for publication January 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Postpulmonary Infarction Syndrome: Case Report

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Pericarditis occurring several days to several months following myocardial infarction is referred to as the Dressler syndrome. This type of pericarditis is often accompanied by fever, a rapid erythrocyte sedimentation rate, and pericardial and pleural effusions. Rarely, pulmonary infiltrations, hemoptysis, arthralgias, myalgias, arthritis, or anemia may also be present. The etiology of this syndrome is unknown, although immune mechanisms have been suggested. Administration of corticosteroids results in its prompt resolution, and the response is so dramatic as to be virtually diagnostic.

Recently, a postpulmonary infarction syndrome was described in three patients who had persistent fever, pleuritic chest pain, and pleural effusion following pulmonary thromboembolism with infarction (1, 2). So reminiscent was this syndrome of the Dressler syndrome that a therapeutic trial of corticosteroids was attempted and achieved a brilliant clinical result.

The patient described in this report illustrates the cardinal features of the postpulmonary infarction syndrome, the difficulty and consequent delay in diagnosis, and the therapeutic and diagnostic efficacy of corticosteroids in achieving a prompt and dramatic resolution of the problem.

Case Report

An eighty-four-year-old woman was admitted to The Mount Sinai Hospital on August 16, 1981 for surgical repair of an intertrochanteric fracture of the right hip. Her past medical history was unimportant except for an undiagnosed, chronic, mild anemia and the use of ten to 12 aspirin tablets daily for many years for arthralgias. Physical examination revealed an elderly white female who was in pain and was moderately tachypenic. The blood pressure was 150/85 mm Hg, the pulse 150/min, and respirations were 22/min. The skin and mucous membranes were pale. The neck veins were engorged at 45°, and rales were heard at both lung bases. The heartbeat was rapid and irregular, and the murmurs of aortic stenosis and mitral stenosis were heard. The right thigh was swollen and the right leg externally rotated. There was a trace of pedal edema.

Significant laboratory findings included hemoglobin, 9.4 g%, with red cell indices revealing hypochromia and microcytosis. The ECG showed atrial fibrillation with a rapid ventricular response. X-ray film of the chest revealed the classical findings of mitral stenosis and bilateral pulmonary congestion (Figures 1, 2). An echocardiogram confirmed the presence of aortic stenosis and mitral stenosis.

Preoperative treatment included digoxin, lasix, and blood transfusion (no source was ever found for the iron-deficient anemia, which was presumed to have resulted from excessive aspirin intake). On August 21 hip surgery was performed without incident. Mini-heparin therapy was begun on August 25. On September 3 the patient developed acute left chest pain, dyspnea, and hypotension, associated with slight tenderness of the right calf. Blood gas analysis revealed P_{O_2} of 64 mm Hg, P_{CO_2} of 23 mm Hg, and pH of 7.5. An x-ray film of the chest on September 3 revealed infiltrate and effusion at the left base (Figure 3), and a lung scan showed bilateral multiple segmental and subsegmental defects unmatched by a ventilation scan. Full heparin therapy was begun.

From September 5 to October 11, 1981 the patient's clinical course was one of severe left chest and left flank pain, daily rectal temperature elevation to 101°F, and x-ray films of the chest showing bilateral fibrotic streaks and a left pleural effusion (Figures 4–7). During those six weeks

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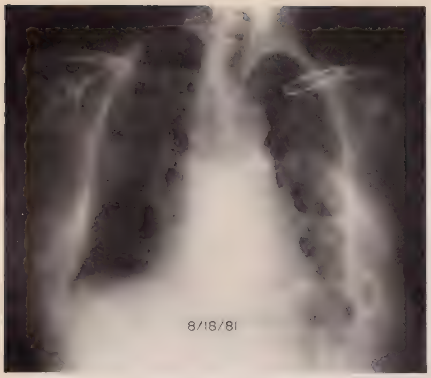

FIG. 1. 8/18/81: Minimal congestive changes and clear left costophrenic sulcus.

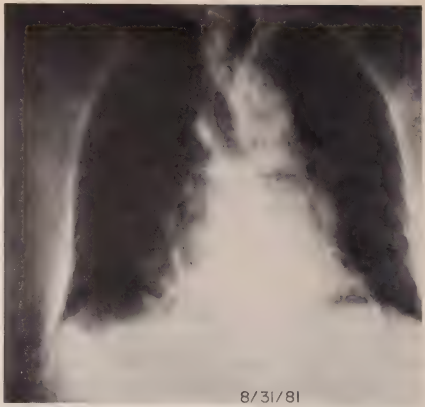

FIG. 2. 8/31/81: Clear lung field and clear costophrenic sulci.

many studies were done to elucidate the cause of the fever and associated findings. The complete blood count, urinalysis, and erythrocyte sedimentation rate findings were normal, as were routine blood chemistries. Immunoelectrophoresis, antinuclear antibody, carcinogenic embryonic antigen, venereal disease research laboratory, T4, antimitochondrial antibody, anti-smooth muscle antibody, and viral antibody titer findings were normal. Results of two abdominal sonograms, two gallium scans, a liver-spleen scan, a bone scan, an abdominal CAT scan, and an intravenous pyelogram were normal. Multiple cultures of urine, blood, stool, sputum, pleural fluid, and cerebrospinal fluid were negative. Multiple potent antibiotics were given alone and in combination with no effect.

On October 12 it was suggested that the patient might have postpulmonary infarction syndrome. Accordingly, 30 mg of prednisone were given daily. The temperature became normal in two days and the pleural effusion vanished by the third day (Figure 8). The dose of prednisone was tapered gradually over two months time; the patient has remained afebrile and pain-free and has clear lung

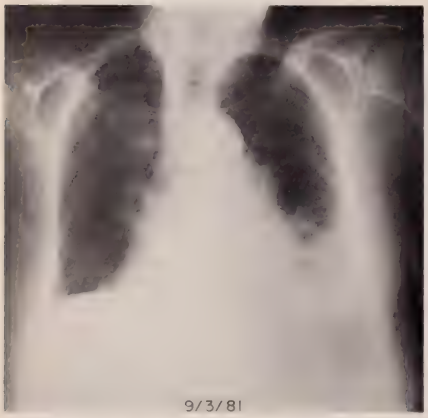

FIG. 3. 9/3/81: Left lower lobe infiltrate and left pleural effusion.

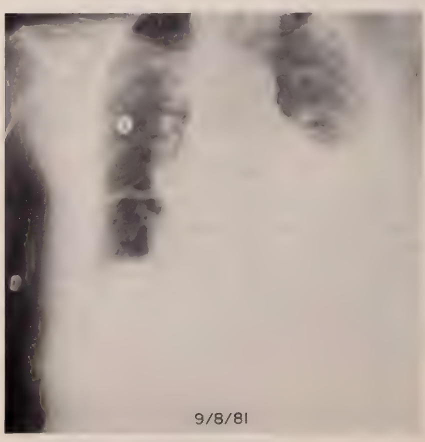

FIG. 4. 9/8/81: Large left pleural effusion with pulmonary congestion.

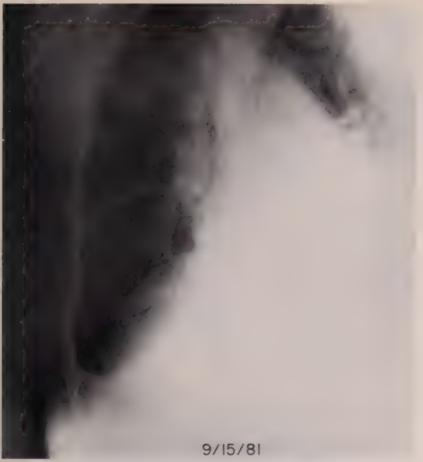

FIG. 5. 9/15/81: Left lateral decubitus film revealing large effusion.

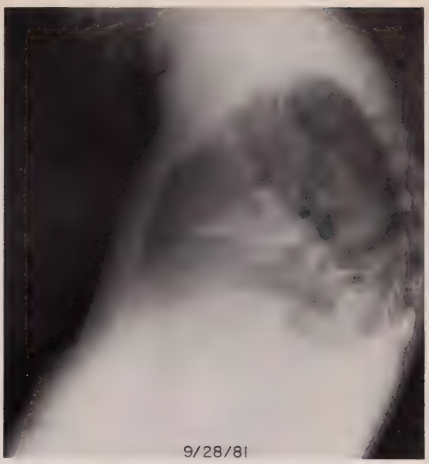

FIG. 6. 9/28/81: Atelectatic streaks with left pleural effusion.

fields radiographically. Current therapy includes digoxin, lasix, and coumadin.

This patient exhibited the classical features of pulmonary thromboembolism with infarction—the sudden onset of chest pain, dyspnea, and hypotension in the setting of prolonged bed rest, hip fracture, and surgery, complicated by the presence of rheumatic heart disease, mitral stenosis, atrial fibrillation, and congestive heart failure. A positive lung scan (Fig. 9), appropriate abnormalities of the blood gases, an x-ray film of the chest showing bilateral atelectatic streaks, and pleural effusion make the diagnosis of pulmonary thromboembolism with infarction unassailable. The diagnosis of postpulmonary infarction syndrome seems equally certain because following pulmonary thromboembolism, the patient developed persistent and prolonged (six weeks) fever, pleural effusion, and chest pain, all of which vanished in a few days with corticosteroid therapy.

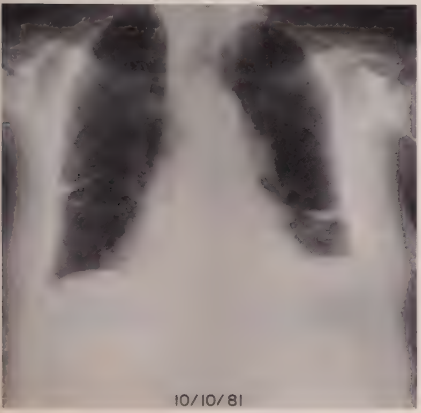

FIG. 7. Atelectatic streaks with left pleural effusion.

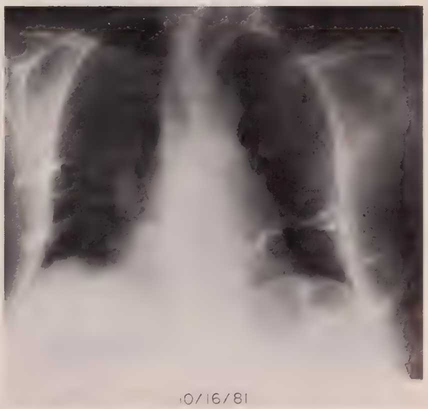

FIG. 8. 10/16/81: Three days after corticosteroid therapy. Note clear left costophrenic angle and sharp delineation of left diaphragm for the first time in six weeks.

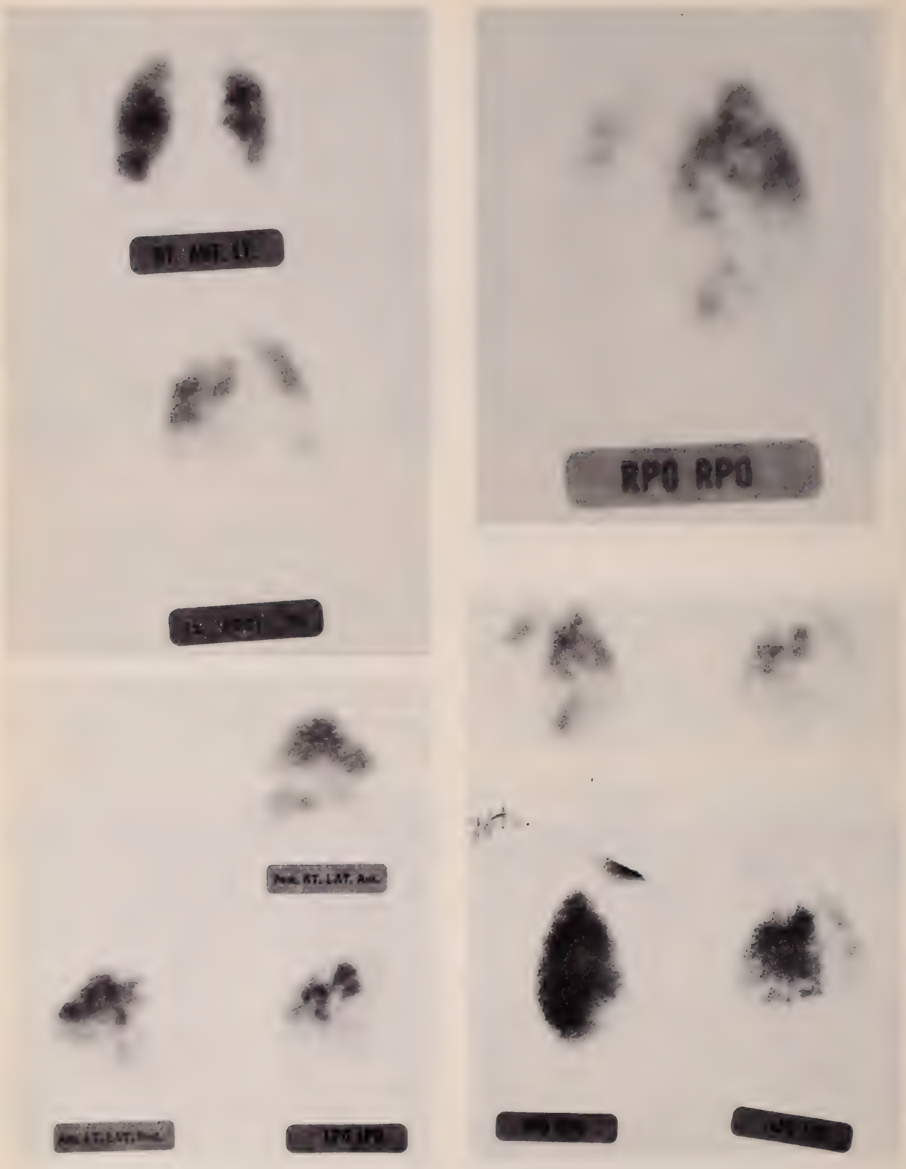
RT. ANT. LT.
RPO RPO
LPO LPO

FIG. 9. Ventilation and perfusion lung scans.

Whatever the pathogenesis of the postpulmonary infarction syndrome may be, recognizing its presence is important so that prompt and proper therapy with corticosteroids may be given, thereby affording the patient dramatic relief and sparing him multiple diagnostic procedures, a protracted hospital confinement, and a staggering expense.

Summary

Three patients have been previously described who developed persistent fever, chest pain, and pleural effusion after pulmonary thromboembolism with infarction. Each responded dramatically to corticosteroid therapy similar to the response of patients with Dressler syndrome.

A fourth patient is now described who developed persistent fever, chest pain, and pleural effusion following pulmonary thromboembolism, and who responded immediately to corticosteroid therapy, thereby lending further credence to the existence of a newly described clinical entity—the postpulmonary infarction syndrome.

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Submitted for publication January 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Orthopaedic Notes

Roger N. Levy, M.D., Editor

This issue of *The Mount Sinai Journal of Medicine* introduces this section, Orthopaedic Notes. Brief reports of cases illustrating fundamental problems as well as current concepts of care will be presented.

The case report in this issue illustrates our current concept of spinal instrumentation in the treatment of paralytic spinal deformity.

ROGER N. LEVY, M.D.

Segmental Spinal Instrumentation at The Mount Sinai Hospital

RICHARD I. ULIN, M.D., AND GEORGE H. MCGINNISS, M.D.

Paralytic scoliosis is a special problem for several reasons (Fig. 1). The trunk may be unbalanced and hinder upper extremity function. Pulmonary and cardiac function may be compromised by the chest deformity and the paralysis which are additive in their effect. Paralytic deformity most often occurs in the immature child. This type of deformity is invariably progressive and responds poorly to nonoperative treatment such as bracing.

Surgical treatment is often necessary but has traditionally been fraught with problems. Tight restrictive casts used preoperatively and postoperatively for external support and correction are contraindicated, as they further decrease pulmonary function. Spinal fusions performed to prevent progression must be very long, over many segments, to control these curves. The pseudarthrosis rate of the fusion has been as high as 20%.

The method of treatment which has evolved attempts to account for these problems (1). Skeletal traction is initiated upon admission to the hospital to obtain correction of the curve preoperatively. A respiratory program is begun. Methods of internal fixation and correction of the spine provide immediate stability and diminish the need for restrictive external support.

The first widely used method of internal fixation of the spine is Harrington rod instrumentation (2). It relies predominantly on one or more distraction rods engaged over the posterior elements at the proximal and distal ends of the curve (Fig. 2).

The problems inherent in such a system are that the forces of correction are concentrated at very small areas distally and proximally (Fig. 3). This is a problem in paralytic patients whose osteoporotic bone tolerates these forces poorly. Hook displacement, especially proximally, and secondary pseudarthrosis continue to be problems. In addition, distraction rods tend to straighten and eliminate the normal postural curves as well as correct the deformity.

It has been apparent that a system of internal fixation that distributes corrective forces segmentally over each vertebra to be included in the spinal fusion and not just at the proximal and distal ends of the fusion would be desirable. A system of this type has been devised by Enrique Luqué of Mexico and it has been demonstrated to be more effective in correcting these clinical problems (3).

The purpose of this report is to present the first

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use of this technique at The Mount Sinai Hospital.

E.P. is an eleven-year-old Indian girl who came to the Neuromuscular Clinic at The Mount Sinai Hospital because of increasing spinal deformity. The patient had polio at the age of six in India. Physical examination revealed that she had a functional 4/5 muscular strength in her upper extremities and a nonfunctional 2/5 muscular strength in her lower extremities. She could eat and care for herself in a wheelchair but could not walk with crutches. She had an 85° right thoracic curve and a 55° left lumbar curve which was unbalanced and not centered over the sacrum. Her pulmonary function was 65%–70% of normal expected values and her arterial blood gas values were within normal limits.

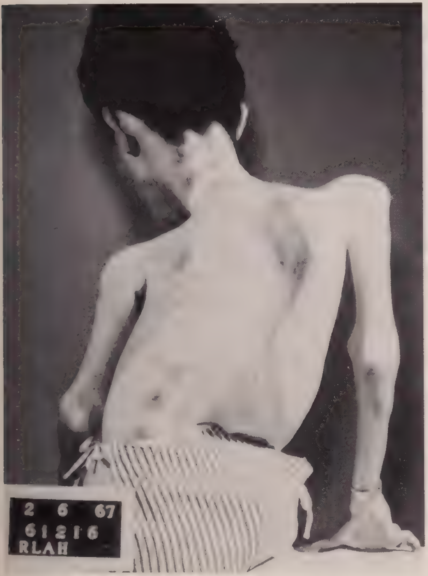

FIG. 1. Paralytic scoliosis—an unbalanced trunk will compromise upper extremity function.

Surgical stabilization and spinal fusion were determined to be the treatment of choice. Initial correction of the deformity was achieved with halofemoral skeletal traction over a three-week period. Surgery consisting of segmental instrumentation with the Luque system of internal fixation from T-3 to the sacrum was performed. A spinal fusion mass of bank bone was then placed over her decorticated posterior elements. Correction was achieved from 85° right thoracic curve to 30°

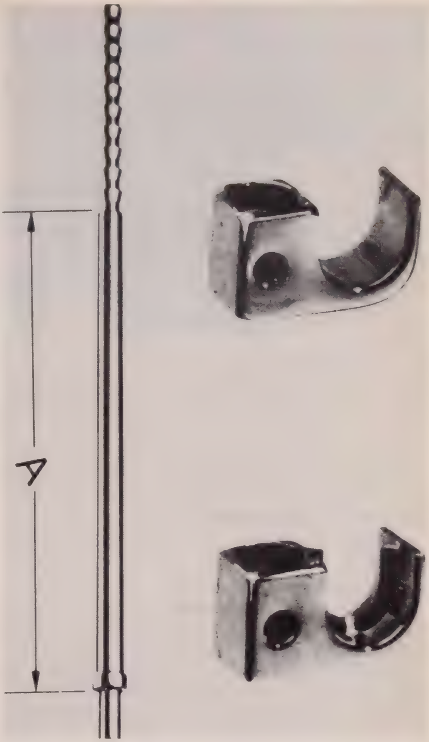

FIG. 2. Harrington distraction rod and two hooks.

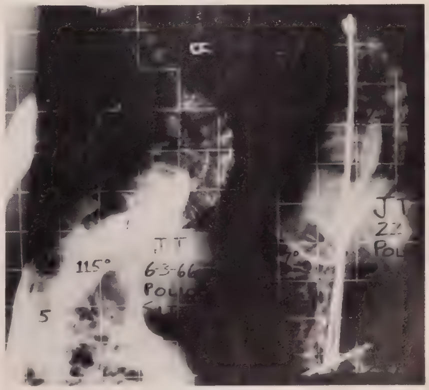

FIG. 3. Preoperative and postoperative x-ray of paralytic scoliosis treated surgically with Harrington system. Two distraction rods are anchored to a sacral bar distally and to a thoracic vertebra proximally.

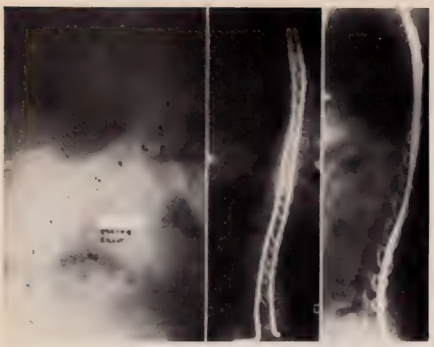

FIG. 4. Paralytic scoliosis treated with Luque system. Note degree of correction on preoperative and postoperative A-P views and preservation of postural curves in lateral postoperative view.

and from a 55° left lumbar curve to 20°. Her spine was centered over the sacrum. The postoperative course was uncomplicated. She was discharged in a light fiberglass body cast three weeks postoperatively sitting without difficulty (Fig. 4).

Discussion

The theoretical advantages of segmental spinal instrumentation have been stated. Less external support is required postoperatively because the system distributes force over such a large area of bone. Using the older Harrington distraction method, the patient would have been obliged to remain recumbent for up to six months postoperatively. Such a program would produce additional osteoporosis and bone weakness. Segmental instrumentation is accomplished by passing sublaminal wires at each vertebral segment in order to stabilize each segment to a pair of prebent rods (Fig. 4). Prebending a rod permits the surgeon to predetermine the degree of correction and to preserve the normal postural kyphosis and lordosis. The disadvantage is that the spinal canal must be entered at every vertebral level of instrumentation. This produces a neurological risk which is greater than that with Harrington rods. Therefore, at Mount Sinai, the use of Luque segmental instrumentation is at present being limited to paralytic patients.

In summary: segmental spinal instrumentation represents a technological advance and an effective method of treatment of the scoliotic curve in the paralytic patient.

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Submitted for publication June 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Neurologic-Neurosurgical Notes

Allan E. Rubenstein, M.D., and Martin H. Savitz, M.D., Coeditors

Hemiballism Secondary to a Metastatic Neoplasm of the Subthalamic Nucleus as Demonstrated by CT Scan

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Abstract

A vascular lesion localized in the region of the subthalamic nucleus is the usual cause of hemiballism. Hemiballism secondary to a metastatic neoplasm is exceedingly rare. When reported, such lesions have only been described at autopsy. We report a case of metastatic adenocarcinoma of the lung, localized to the subthalamic nucleus, as seen on CT scan. We believe this to be the first such instance reported and discuss the anatomy, pathology, and treatment of this uncommon involuntary movement disorder.

Vascular changes, ischemic or hemorrhagic, involving the subthalamic nucleus or its connections are the usual cause of hemiballism. On rare occasions, destructive tumors, usually metastatic, of this region of the brain have been found to be the underlying cause. Such instances have only come to light at autopsy, not being demonstrable during life.

We have recently evaluated a patient with left hemiballismus who on CT scan showed an exquisitely localized neoplasm in the region of the right subthalamic nucleus. On further study, the patient was found to have a primary lung tumor. To our knowledge, this is the first report of a subthalamic metastasis diagnosed during life by CT scan.

Case Report

A 64-year-old right-handed Chilean woman with a 20-year history of hypertension and chronic insomnia was well until five months prior to her admission at The Mount Sinai Hospital. At that time she first noted paresthesias of the left middle finger. Over the following month, she began losing control of the grip in her left hand. Her fingers and wrist began to move involuntarily; gradually this spread to the left shoulder, the elbow, and then the left toes, foot, and leg. Involuntary movements of the face also began at this time. Her speech became slower and she had difficulty in modulation. Occasionally the right lower extremity felt cooler to touch than the left.

The patient suffered from chronic insomnia, "nervousness," and headache. About eight months prior to admission, the headaches changed in character and she began to feel a pressure sensation, which finally localized on the right side. The patient was treated with various anti-anxiety agents, including diazepam, imiprimine, and haloperidol. She received sulpiride, 50 mg a day, for three months; this was discontinued at the time of emergence of the involuntary movements (although whether they preceded or were precipitated by stopping the drug is unclear). She lost eight pounds in the three months prior to admission.

The patient smoked half a pack of cigarettes a day for thirty years and had undergone four breast biopsies from 1965 to 1979 for "benign papillomas." Additionally significant in her history was a pulmonary embolus in 1955 and a renal stone

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This work was supported in part by grants NS11631-10 from the Clinical Center for Research in Parkinsonism and Allied Diseases and RR-71 from the Division of Research of the National Institutes of Health.

in 1960. Both parents died of cerebrovascular accidents.

Her initial examination at The Mount Sinai Hospital revealed blood pressure of 164/100 and resting pulse of 80. The general physical examination was unremarkable. Neurological examination revealed an alert, well-oriented woman with intact recall and no aphasia. Speech was slightly halting. The optic discs were sharp with some vascular narrowing. There was no field cut to confrontation. The pupils were 2 mm OD and 3 mm OS and were reactive to light and accommodation. Extraocular movements were full without nystagmus, optokinetic nystagmus was normal, and corneal reflexes were intact. There were involuntary facial dyskinesias noted on the left, primarily around the mouth. Facial strength was normal. The palate elevated symmetrically, and the gag reflex was normal. The tongue was midline. Power was normal in all four extremities. The left upper extremity was notable for spontaneous involuntary choreatic/ballistic movements. These consisted of spontaneous irregular rotation on the left ankle and occasional flinging movements of the left leg. Rapid alternating movements on the right were normal but they induced choreic movements on the left side. There was no ataxia. The gait was remarkable for increasing the left-sided chorea/ballism. The patient was unable to tandem walk. The sensory examination was unremarkable. The muscle stretch reflexes were 2+ symmetrically in the upper extremities, 2+ knee jerks bilaterally, and trace-to-absent ankle jerks. The toes were downgoing bilaterally.

The hemoglobin was 14.0 gm%, the hematocrit 41.4%, and the white blood cell count 7,600, with 56% polymorphonuclears, 31% lymphocytes, and 8% mononuclears, and 3% eosinophils. The SMA-18 channel was entirely normal, as was the thyroid function test, VDRL, and erythrocyte sedimentation test.

Chest radiogram demonstrated left upper lobe density with deviation of the trachea. Mammography showed a round density behind the right nipple 1 cm behind the skin with definitive ducts and faint calcifications in the duct wall. There was possible distention of the ducts and no definitive evidence of malignancy.

The electromyogram was normal and nerve conduction studies were remarkable for slightly reduced amplitude in the lower extremities and absence of the H reflex in the gastrocnemius muscles bilaterally. On lumbar puncture, opening pressure, cell count, glucose, and chemistry results were normal. Cytologic findings were negative.

CT scan of the head revealed an exquisitely localized ring-enhancing lesion in the right subthalamic nucleus (Figure 1). Also noted were a ring-enhancing lesion in the right occipital region with surrounding edema and right-sided frontal and left occipitoparietal enhancing densities.

Biopsy of the lung lesion confirmed a diagnosis of adenocarcinoma.

The patient was begun on phenytoin 100 mg three dimes a day and dexamethasone (Decadron) 4 mg four times a day. In the initial period after beginning Decadron, there seemed to be improvement of the intensity and frequency of the left hemiballism. The patient subsequently received a course of 3,000 rads of radiation therapy to the whole brain.

A repeat CT scan showed persistence of the right frontal and occipital lesions. The left occipitoparietal lesion was not seen. The left subthalamic lesion was dramatically reduced in size (Figure 2). Despite this, the ballistic movements, which had diminished, returned to their original intensity. Further treatment with reserpine or tetrabenazine to control her abnormal movements was recommended to her physician.

Discussion

Hemiballism has long been associated with lesions in the region of the corpus Luysii (1, 2). Although rare cases of hemiballism have been reported with lesions outside the subthalamic nucleus (3–5), these are notable as the exceptions. Experimental lesions in the subthalamic nucleus

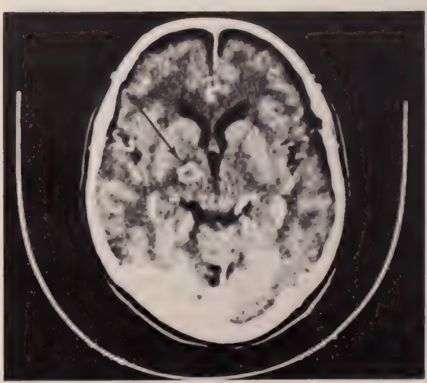

FIG. 1. Contrast-enhanced CT scan demonstrating ring-enhancing lesion in the right subthalamic nucleus (arrow).

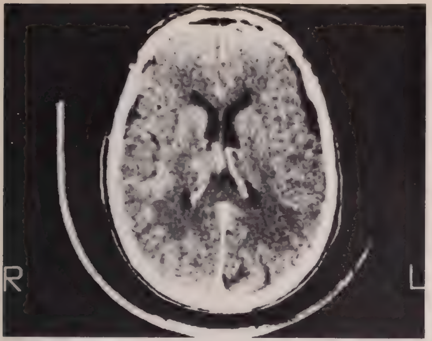

FIG. 2. Contrast-enhanced CT scan demonstrating marked reduction of enhancing lesion in right subthalamic nucleus.

of primates have provoked the only reproducible dyskinesias similar to those seen in humans, hemichorea/hemiballism (6). On occasion, thalamotomy attempted for other extrapyramidal disorders has resulted in hemiballism, the surgical lesion being found in the region of the corpus Luysii (7).

Whether damage to the subthalamic fiber pathways alone can invoke ballism is not known for certain, but has been postulated (8). The afferent and efferent pathways themselves are only now being clarified. The difficulties encountered in trying to establish the subthalamic connections are related to the multiple fiber systems surrounding and even traversing this area (for example, the nigrostriatal fibers).

The primary afferent fibers arising from the external globus pallidus are carried in the subthalamic fasciculus. Afferent fibers are also derived from the cortex (9) and the substantia nigra, dorsal raphe nuclei, locus ceruleus, and pedunculo-pontine nucleus (10). The major efferent fibers return to both the internal and external globus pallidus (11).

Ballism will appear if approximately 20% of the subthalamic nucleus is destroyed (2), although it may result from destruction of a smaller total volume if fibers of the subthalamic fasciculus are interrupted (12); its appearance and perhaps its severity is dependent upon preservation of the pallidal outflow tracts (13). It may be modified by lesions either downstream (thalamus, cortex, or corticospinal tracts) or of the pallidum, and may be modified by the striatal pathways (14–16).

Hemiballism secondary to focal metastatic disease has been reported only rarely (13, 17–21). All were found at postmortem. We add the present case, which is the first to our knowledge to be visualized on CT scan.

CT scanning has been effective in diagnosing vascular lesions in ballism (5, 16). Melamed et al (22) described a case of hemiballism secondary to a focal hemorrhage in the contralateral subthalamic nucleus as seen on CT scan. Hemiballism due to a metastatic neoplasm in this location has not been previously reported. The present case is notable in that the CT scan not only localized a mass lesion in the appropriate brain region but prompted further studies which led to a definitive diagnosis. Though multiple cerebral lesions were found, the only one producing symptoms was in the subthalamic region.

In the present case, it is impossible to state with certainty the extent of damage to the afferent and efferent pathways. Furthermore, despite the impressive diminution in the size of the lesion (Fig. 2), the movements persisted. This suggests that at least 20% of the subthalamic nucleus was destroyed (perhaps beyond the resolution of the CT scan). Carpenter et al found that there was no correlation between severity and persistence of the movements, provided there was a minimum volume loss of 20% (12). Our patient's initial improvement with steroid therapy suggests that the intensity of the movements may have been related to pressure from the surrounding edema. It is unlikely that the diminished force of the ballistic movements was due to progressing destruction of the pallidofugal fibers, as the movements again increased during radiotherapy.

The number of pharmacological agents which have been implicated in inducing dyskinesias and in their control warrants comment. A number of unrelated substances have been reported to ameliorate hemiballism. However, the natural history of this dyskinesia, especially when induced by vascular accident, is far from clear. Early reports (2) predicted a universally poor outcome, with persistence of the movements and an early demise. Conversely, Hyland and Forman (23) reported spontaneous recovery in 8 out of twelve cases due to cerebrovascular accidents. Complete cessation occurred between 5 days and 3 months.

In the present case, one can only speculate as to the role of sulpiride in either masking or stimulating the dyskinesia. Sulpiride and tiapride have been reported of value in senile chorea/ballism (24). However, it is now recognized that substituted benzamides can induce both acute and tardive dyskinesias (25). Phenytoin apparently had little effect on the dyskinesia in this case. It has been reported to induce (26) and to alleviate (27, 28) chorea. Deanol has been reported to be effective in treating a single case of ballism (29), but its effectiveness is doubted and was not used in this instance.

Neuroleptics (chlorpromazine, haloperidol, perphenazine) have been used successfully in cases of hemiballism secondary to vascular lesions (30, 31). However, haloperidol has also been reported to exacerbate hemiballism (32). Obeso (33) reports a patient who became symptomatically worse over 48 hours while being treated with haloperidol, but improved on reserpine (although this patient was on a higher dose than was used by Klawans et al). Reserpine, a central dopamine depletor, offers the advantage of long-term use without the risk of inducing tardive dyskinesia (34). In the case of hemiballism due to metastatic carcinoma reported by Lemmon (21), the patient did not respond to either chlorpromazine or reserpine. Tetrabenazine depletes CNS dopamine in a manner similar to reserpine (by blocking the storage granular uptake of intraneuronal dopamine). It may also have dopamine receptor blocking action as well (35). Tetrabenazine has been used effectively in hemiballism (36, 37). Finally, Lenton (38) has reported a case in which neither tetrabenazine nor haloperidol was successful, and the patient's hemiballism was controlled with sodium valproate (200 mg three times a day). A second case has recently been reported by Chandra (39). The role of valproate in augmenting CNS gamma-aminobutyric acid is controversial (40). A trial of reserpine was undertaken in the present case without dramatic improvement.

Although the pathophysiology of hemiballism is not yet clearly understood, the CT scan in the present case highlights the anatomic relationship of this dyskinesia, described by Martin in 1927 as the "syndrome of the Body of Luys" (1).

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Submitted for publication June 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Student's Corner

Barry Berson, B.A., Editor

Cholecystectomy and Large-Bowel Cancer: Is There a Relationship?

JAMES BIANCO, B.S., M.D.

Based on the geographic and socioeconomic distribution of colorectal cancer, migrant population studies, retrospective studies of American and Japanese patients with large bowel cancer, and the dietary habits of different risk populations, it is generally accepted that diet, particularly when high in fat and beef, is a major etiologic factor in colon cancer (1–5). Wynder et al (5) first proposed that the incidence of colon cancer is mainly associated with dietary fat and further suggested that dietary fat influences the composition of the fecal flora, which may be involved in the pathogenesis of colon cancer. Some of the known carcinogens or cocarcinogens might be produced in the gut by bacterial action on dietary components or on secretions produced in response to the diet (6).

It has been postulated that bacteria can produce carcinogens or cocarcinogens from bile acids in particular. Full aromatization of the bile acid nucleus would yield a cyclo-pentaphenanthrene. The carcinogenicity of these compounds has been reviewed by Coombs and Croft (7). Only four types of nuclear dehydration reactions are theoretically needed to achieve this full aromatization (8), and these have all now been demonstrated using human gut bacteria (9–12). Three of these reactions are carried out almost exclusively by nuclear dehydrogenating clostridia. There is, however, some disagreement concerning the role of bile salts in relation to the development of large bowel cancer (13, 14).

Cholecystectomy alters bile salt metabolism (15) and results in a more frequent turnover of the bile salt pool (16). Due to increased exposure of primary bile acids to colonic bacteria, formation of secondary bile acids (deoxycholic and lithocholic acids) is increased (15). After cholecystectomy, the colonic mucosa is exposed to more secondary bile acids which might be carcinogenic. If the bile salt hypothesis (17) is true, the incidence of large bowel cancer should be increased among cholecystectomized patients. This paper reviews the pathogenesis and the studies undertaken to support this hypothesis.

Discussion

Conjugated bile salts are secreted by the liver and stored in the gallbladder. With each meal, the gallbladder contracts and the bile salt pool enters the intestine. Most of this pool is reabsorbed, but before this can happen some bile salts are attacked and altered by bacteria in the ileum and colon. Several authors (6, 10, 18, 21) hypothesize that cholecystectomy in humans results in the following pathophysiological changes: (a) continuous passage of the bile salt pool through the liver and intestine; (b) in the absence of the gallbladder, the bile salt passes through the intestine constantly throughout 24 hours, whereas in patients with a functioning gallbladder this only occurs during digestion; (c) increased exposure of the primary bile salts to intestinal bacteria, resulting in increased dehydroxylation and, hence, increased proportion of deoxycholic acid in the total bile salt pool; and (d) increase in or modification of bacterial enzymatic reactions on the bile salt pool as a result of the increased stasis and modifications of the constituents of the bile salt pool. These authors believe that all or some of these four changes can have a promoting or accelerating effect on colon carcinogenesis.

In an experimental study, Werner et al (19) investigated the influence of cholecystectomy on the development of carcinoma of the colon in mice. The results indicated a possible cocarcinogenic ef-

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This paper was written when the author was a third-year student at the Mount Sinai School of Medicine.

fect of cholecystectomy as a result of increased production of secondary bile salts by colonic bacteria and failure of the gallbladder to reabsorb some carcinogenic substances passing through the liver (19). Inhoffen (20) reviewed the structural similarity between steroids and the polycyclic aromatic carcinogens and showed that deoxycholic acid can be converted chemically into the very potent carcinogen 20-methyl-cholanthrene via dehydronorcholene. Dehydronorcholene is not carcinogenic but can be converted into a carcinogenic metabolite by the action of intestinal bacteria (20).

The relation between prior cholecystectomy and right-sided colon cancer was investigated in a case-control study (22) of 150 patients with histologically confirmed adenocarcinoma of the cecum or ascending colon, and of two comparison groups. One comparison group consisted of 150 patients matched for age, sex, and race who had histologically confirmed adenocarcinoma of the sigmoid. The other comparison group consisted of 123 neighborhood controls. Compared with left-sided cancer controls, the right-sided colon cancer cases had a relative risk of 1.87 for colon cancer after cholecystectomy. The relative risk was 1.86 when the right-sided colon cancer cases were compared with the neighborhood controls. When compared with both control groups, the 150 cases had a relative risk of 1.77, with 95% confidence limits of 0.95 and 3.3 ($p = 0.07$). The authors (22) concluded that the increased risk of right-sided colon cancer after cholecystectomy may be associated with changes in biliary metabolism occurring after removal of the gallbladder.

In a matched case control study (23) conducted to determine the association between previous cholecystectomy and the development of large bowel cancer, 160 men and 145 women with large bowel carcinoma were studied. One control was selected for each case matched according to age and sex. No association was found among male patients but for women an estimate of relative risk of 2.7 was obtained for patients who had had previous cholecystectomy. The authors were not, however, able to explain why the association was confined to women only.

The findings of these and other authors (19, 21, 29) are supported by clinical observations and animal studies. Capron and associates (24) compared the frequency of prior cholecystectomy in 237 patients operated on for colonic cancer with 2,458 necropsy cases who were free of cancer. They found that the frequency of prior cholecystectomy in women with colonic cancer was significantly higher than that in necropsy controls (13% vs. 3.3%).

Conclusion

All the studies mentioned above involved hospital or necropsy cases and controls in which some selection bias could have operated in producing the observed results. Such Berksonian bias could indeed have produced an association when a real one did not exist. On the other hand, there is increasing evidence, discussed above, of a relationship between bile acid metabolism and carcinoma of the colon. It might be considered that the right side of the colon is most likely to be affected by the potential carcinogenic effect of certain bile acid metabolites. The risk of right-sided colon cancer following cholecystectomy, even if the relationship is real, would still be relatively small. However, it is important to note this relationship and use this information to further understand the etiology of colon cancer.

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Submitted for publication June 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 4, July–August, 1983
Printed in U.S.A.

Student's Corner

Barry Berson, B.A., Editor

Cholecystectomy and Large-Bowel Cancer

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Abstract

To determine the relationship between prior cholecystectomy and the development of large-bowel cancer, the medical records of 69 men and 61 women with large-bowel cancer were reviewed for evidence of previous cholecystectomy. A relative risk of 5.66 was found for right-sided compared to left-sided colon cancer patients and 2.48 for female compared to male patients. These data support findings in the literature that right-sided colon cancer patients and women have an increased risk of developing colon cancer after cholecystectomy.

Colorectal cancer is the most common visceral cancer in the United States. It is the second most common cause of cancer mortality, which is responsible for 40,000 to 50,000 deaths annually.

Epidemiologic data suggest a correlation between high intake of fats and cancer of the colon. Dietary fat stimulates the secretion of bile acids in the large bowel. Anaerobic organisms such as clostridia and bacteriodes in the colon modify the bile acids chemically into potential carcinogens or cocarcinogens (1). Certain strains of clostridia, nuclear dehydrogenating clostridia, are able to dehydrogenate the primary bile acids, yielding secondary bile acids, deoxycholic and lithocholic acids, which are known to be carcinogenic in animals (2, 3). Fecal specimens from populations in Western countries, where there is a high incidence of colon cancer, contain higher concentrations of secondary bile acids than specimens from populations in African and Eastern countries, where there is a low incidence of colon cancer (4). Similarly, fecal concentrations of secondary bile acids in patients with cancer of the colon are higher than fecal concentrations of the same bile acids in patients without such cancer (5).

Cholecystectomy alters bile salt metabolism. The primary bile salts, cholate and chenodeoxycholate, are reduced, while deoxycholate remains normal (6). This increase in the proportion of secondary bile acids is due to the increased enterohepatic recycling and degradation of primary bile acids by intestinal microorganisms (7). After cholecystectomy the large bowel mucosa is therefore exposed to a more motile and chemically altered bile salt pool or to its carcinogenic metabolites.

This study was undertaken to investigate the relationship of prior cholecystectomy and colon cancer.

Mechanism of Colorectal Carcinoma. It is generally agreed that diet is of etiologic significance in the development of colorectal cancer, particularly the levels of dietary animal fats and consequent concentrations of fecal bile acids and steroids (8), the anaerobic flora of the large bowel (9), and dietary fiber content (10).

Wynder et al (11) postulated that diet determines the composition of the bacterial flora of the gut, which in turn produces cocarcinogenic or carcinogenic compounds. People living in areas with a high incidence of colon cancer have a high-fat and high-animal-protein diet, whereas those who live in areas with a low incidence of colon cancer live on a low fat diet with little animal protein. The former have a fecal flora containing relatively large numbers of anaerobes, whereas the latter have a fecal flora rich in aerobic streptococci and enterococci.

Anaerobic bacteria metabolize steroids more actively than the aerobes. Fecal excretion of cholesterol metabolites, coprostanol and coprostanone, as well as bile acids, was higher in groups

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This paper was written while the author was a fourth-year student at the Mount Sinai School of Medicine.

with a high fat diet than in low-fat-diet groups. Hill (1) hypothesized that qualitative and quantitative differences in luminal compounds such as bile acids and cholesterol metabolites play an important role in colon carcinogenesis. Animal model experiments indicate that deoxycholic and lithogenic acids act as colon tumor promoters (2, 3, 12).

Many strains of anaerobes, in contrast to *Escherichia coli*, possess the enzyme cholanoyl hydrolase, which enables them to dehydrogenate the 7α hydroxyl group of bile acids, converting cholic acid to deoxycholic acid and chenodeoxycholic to lithogenic acid. The activity of this fecal 7α-dehydroxylase and fecal cholesterol dehydrogenase, which converts cholesterol to coprostanol, is higher in patients with colon cancer than in controls (13).

Effects of Cholecystectomy on Bile Acid Metabolism. The gallbladder stores bile. Following cholecystectomy, the bile acid mass recycles more frequently because of the absence of storage. Liver synthesis of bile salt is homeostatically controlled by the amount of absorbed bile salts returning to the liver via the portal blood (14, 15). This mechanism becomes active during both fasting and feeding after cholecystectomy. Hepner et al (16) compared the bile acids pools in patients with cholecystectomy, patients with cholelithiasis, and healthy controls. They found that cholecystectomized patients had a deoxycholic acid pool larger than the healthy controls.

Cholecystectomy causes reduction of the two primary bile acids, cholic and chenodeoxycholic, while the deoxycholic acid pool remains normal (6, 7). As a result, the total bile salt pool is reduced to almost half normal and deoxycholate becomes the predominant bile salt. The increased enterohepatic cycling of bile acids after cholecystectomy increases the exposure of primary bile acids to intestinal bacteria. Since dehydroxylation is essentially a function of the colonic flora and the bile salt pool spends a greater amount of time with colonic bacteria, 7α-dehydroxylation is enhanced and so the proportion of secondary bile acids is increased.

Relationship of Cholecystectomy and Colon Cancer. Cholecystectomy increases the proportion of secondary bile salts because of increased bacterial degradation from an increased enterohepatic circulation. It has also been suggested that carcinoma of the colon is caused by increased production of secondary bile salts when the bowel transit time is reduced by a low-residue Western diet. Hence the hypothesis that cholecystectomy predisposes to the development of carcinoma of the colon. However, this hypothesis was suggested only recently and the literature on this topic is scanty.

Turnbull et al (17) reported a 45-fold increased colon cancer risk following cholecystectomy in patients with large bowel cancer admitted between 1968 and 1972 to Wellington Hospital, New Zealand. Of the colon cancer patients, 12% of the women and 3% of the men had had a previous cholecystectomy. Turnbull et al pursued a followup, a matched case-control study of 160 men and 145 women (18). No association was found among male patients, but for women a relative risk of 2.7 was found for patients who had had a prior cholecystectomy.

Capron et al (19) compared the frequency of previous cholecystectomy in 237 patients who had colon cancer and 2,458 autopsy cases free of cancer. They found 13% of the women with colon cancer had had a prior cholecystectomy, whereas the control group was 3.3%. They agree with Turnbull that women seem to have a higher risk. In addition, the frequency of previous cholecystectomy was found to be higher in cancer patients with right-sided lesions than left-sided lesions. Vernick et al (20) examined this finding by reviewing 706 cases of large bowel cancer grouped by subsite, sex, and age identified during the Third National Cancer Survey. There was a gradient of previous cholecystectomy frequency from 10.5% in ascending colon cancer cases to 2.1% in rectal cancer cases. Vernick and Kuller (21) later conducted a case-control study of 150 patients with right-sided colon cancer and a group of 150 patients matched for age and sex with left-sided cancer patients, as well as 123 neighborhood controls. The patients with right-sided cancer, when compared to those with left-sided cancer, had a relative risk of 1.87 for prior cholecystectomy. When compared with the controls, the relative risk was 1.86. They confirmed the conclusion of Vernick et al (20) that a positive association exists between cholecystectomy and right-sided colon cancer.

Linos et al (22) conducted a cohort study of 460 male and 1,221 female patients who underwent cholecystectomy during 1950 at the Mayo Clinic. Carcinoma of the colon was found to develop in a higher than expected number of patients. The association was significant only in women (relative risk of 1.7) and right-sided colon cancer patients (relative risk of 2.1).

Methods

The present study intends to examine the relationship of prior cholecystectomy and colon cancer as reported in the literature. The medical records of 168 patients with a discharge diagnosis of large bowel cancer during the period January through June 1979 at Mount Sinai Hospital were reviewed. Among these, four patients had a history of chronic ulcerative colitis, one had villous adenoma, and 33 either were first admitted with large bowel cancer at another hospital or were first diagnosed prior to the admission under study. They were all excluded from the study. The pathology reports of the remaining 130 patients were reviewed to ascertain the diagnosis of colorectal cancer. The cancer was staged according to Dukes' classification.

The following variables were recorded: age, sex, date of first admission with colon cancer, site of cancer, pathology of cancer, and year of cholecystectomy if this operation had been performed prior to the diagnosis of cancer. Records associated with all admissions were also reviewed. If no mention was made of prior cholecystectomy, it was assumed that the patient had no prior cholecystectomy. The colon cancer was classified as right-sided cancer (hepatic flexure, cecum, ascending colon, transverse colon), left-sided cancer (splenic flexure, descending colon, sigmoid, rectosigmoid), or rectal cancer.

Results

A total of 130 colorectal cancer patients, 69 men and 61 women, were included in the study. Of these, 23 patients (8 men and 15 women) were found to have had cholecystectomy in the past (Table I). Table II gives the distribution of colorectal cancer by subsite categorized in patients with and without prior cholecystectomy.

The proportion of women having a prior cholecystectomy was 25% (15:61) compared to 12% (8:69) in men. There was a gradient of previous cholecystectomy from right-sided colon cancer (40%) to left-sided colon cancer (12%) to rectal cancer (7%). Table III shows the relative risk of right-sided colon cancer associated with prior cholecystectomy when compared to left-sided colon and rectal cases (5.66); also, the relative risk of female colorectal cancer patients with prior cholecystectomy when compared to the male patients (2.48).

TABLE I
Sex Distribution of Colon Cancer Patients

Prior Cholecystectomy	Males	Females	Total
+	8 (12%)	15 (25%)	23 (18%)
−	61	46	107
Total	69	61	130

TABLE II
Distribution of Colon Cancer by Subsite

Prior Cholecystectomy	Right-sided Colon	Left-sided Colon	Rectum
+	13 (40%)	8 (12%)	2 (7%)
−	20	60	27
Total	33	68	29

The temporal relationship between the time of cholecystectomy and the first diagnosis of colon cancer for the right-sided colon, left-sided colon, and rectum is presented in Table IV. In only one instance was the cholecystectomy done less than two years before diagnosis of the cancer. All the other cases had a time interval of five or more years. The mean interval was 16.3 years and the median was 15.

Table V shows the distribution by stage (Dukes' classification) of colorectal cancer at the first diagnosis after cholecystectomy. The majority (19:23) were in the advanced stages C and D.

Discussion

There was a gradient of previous cholecystectomy frequency from right-sided colon (40%) through left-sided colon (12%) to rectum (7%) which was in agreement with the findings by Vernick et al (20). But the low rate of occurrence of rectal cancer was in conflict with the finding by Turnbull et al (18) that prior cholecystectomy has an association with rectal cancer. Other studies (19–22) have shown that right-sided colon cancer has a stronger association with prior cholecystectomy than left-sided colon cancer. The present study supports this view, finding a relative risk of 5.66 ($p < 0.001$) when right-sided and left-sided colon carcinomas are compared.

There are several explanations for this higher relative risk of right-sided colon cancer after cho-

TABLE III
Relative Risk of Colorectal Cancer by Sex and Subsite

	Prior Cholecystectomy		
Risk Factor	+	−	Relative Risk
Sex			
Females	15	46	2.48 $p < 0.05$
Males	8	61	
Subsite			
Right-sided colon	13	20	5.66 $p < 0.001$
Left-sided colon & rectum	10	87	

TABLE IV

Interval between Cholecystectomy and Colon Cancer Diagnosis by Subsite

Interval (year)	Right-sided Colon		Left-sided Colon		Rectum	
	No.	Cum. Freq. %	No.	Cum. Freq. %	No.	Cum. Freq. %
2	1	8	0	0	0	0
2.1–8.0	2	23	4	50	0	0
8.0–16.0	3	46	1	63	0	0
16.1	7	100	3	100	2	100

lecystectomy. First, higher levels of secondary bile acids with their carcinogenic potential are absorbed more proximally (in the right colon) than distally. Malhotra (23) noted that in a cholecystectomized patient, the bile, instead of turning neutral through loss of water and bicarbonate and staying inside the gallbladder, dribbles into the duodenal lumen with an alkaline content. He stated that the intracellular mucus of the mucus cells escapes in an alkaline medium and will cause damage. This type of cellular damage enhances mitotic activity and marked hyperplasia, which may predispose to neoplasia. The right side of the colon may have more contact with this alkaline bile than the left side, since more bile is absorbed proximally.

Second, Barker (24) raised the possibility of an "ascertainment" bias; that is, patients who have had cholecystectomy are more likely to be investigated for future gastrointestinal symptoms, particularly on the right side of the abdomen. He postulated that asymptomatic right-sided colon cancer cases are more likely to be detected earlier.

Third, Vernick et al (20) stated that a spurious relationship may exist between prior cholecystectomy and ascending colon carcinoma. Since the prevalence of asymptomatic gallbladder disease is high, they pointed out the possibility that a patient may have both asymptomatic gallbladder disease and colon cancer simultaneously. A cholecystectomy is then performed and a diagnosis of right-sided colon cancer is made later. In this study, only one patient had a cholecystectomy less than two years before the diagnosis of colon cancer; all other cholecystectomies were performed at least five years before the diagnosis. Thus it seems unlikely that the missed diagnosis accounted for the higher incidence of cholecystectomy with right-sided colon carcinoma.

TABLE V

Distribution of Postcholecystectomy Colorectal Cancer Cases Dukes' Classification

Stage	Males		Females		Total	
	No.	(%)	No.	(%)	No.	(%)
A	0	(0%)	0	(0%)	0	(0%)
B	1	(12%)	3	(20%)	4	(17%)
C	5	(63%)	7	(47%)	12	(52%)
D	2	(25%)	5	(33%)	7	(31%)
Total	8		15		23	

Virtually all studies (17, 19, 20–22) show a strong association between prior cholecystectomy and colon cancer in women. The present study confirmed the finding that the relative risk associated with prior cholecystectomy for female colon cancer patients was higher than for males (2.48, $p < 0.05$). However, it is difficult to explain this finding. If the studies by Barker (24) and Vernick et al (20) are valid, and given that in general middle-aged women have a higher incidence of gallbladder disease than the rest of the population, perhaps they receive closer medical scrutiny than male patients.

There may be other explanations for the association between prior cholecystectomy and colon cancer. Previous surgery itself could be implicated; but this is unlikely since it has been shown (25) that various surgical procedures (appendectomy and others) do not increase the risk of developing colon cancer. Another hypothesis is that gallbladder disease is associated with an increased risk of colon cancer. This implies that the association between cholecystectomy and colon cancer is a mere reflection of an association between cholelithiasis and colon cancer. Doouss et al (26) examined 1,257 autopsy records and found that of 40 subjects with carcinoma of the large bowel, 10 had associated gallstones. This incidence was not significantly different from the incidence in the group as a whole. Castleden et al (27) conducted a retrospective study, comparing 342 patients with large bowel cancer, 342 patients with diverticular disease of the colon, and 342 patients without either disease to assess the incidence of gallstones. Forty-three of 342 patients with carcinoma of the colon (12.6%) and 38 of 342 controls (9.4%) were noted to have gallstones. Both studies concluded that there was no association between gallstones and carcinoma of the colon.

The present study confirms the view that female and right-sided colon cancer patients have a higher association with prior cholecystectomy than male and left-sided colon cancer patients.

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Submitted for publication October 1982.

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The Mount Sinai Journal of Medicine
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Tribute to Thomas C. Chalmers, MD

Only a few healthy souls, lucky enough never to have been sick, or spaced out enough to think they never will be, would doubt that running a world-class academic medical center *and* superintending a top-flight school of medicine is a full day's work. For the past ten years Dr. Thomas C. Chalmers has done just that, each day, every day, as president of The Mount Sinai Medical Center and dean of the Mount Sinai School of Medicine of The City University of New York. His has been a task of construction. Yet the only building that has risen during his tenure, start to finish, is the parking garage. As much as the faculty esteems this accomplishment, we honor him today for a much more meaningful type of construction. He has built the most fragile of human structures, the intellectual climate, with bricks of integrity and mortar of spirit, lifting the integrated Mount Sinai, school and hospital, to a new magnitude of brilliance.

At times Dr. Chalmers has served as architect of this enterprise, insisting, for example, on a new Department of Biomathematical Sciences so as to guarantee orderly systems of thought and analysis. It has often been said that scientific prestige is inversely proportional to the size of the object on which the scientist works. Alas, general physicians are near the bottom of this list, working as they do on patients. Specialists work on organs. Chemists who work on molecules rank right up there in the hierarchy, just beneath physicists who work on particles. Mathematicians are considered to occupy the pinnacle, because they don't work on anything at all. We expect this state of affairs to change after a year of sabbatical reconstitution and retooling, when Dean Chalmers will become Distinguished Service Professor Chalmers and return to Mount Sinai to apply his personal mathematics and critical analysis to clinical medicine. He can be well schooled in this by his predecessor, Dr. Hans Popper, who is still as vigorous as any man on the faculty.

At times instead of architect, the dean has served as gang boss, recruiting the best available minds to lead the faculty in the several departments of the school and hospital. He sought out people who are discontent, discontent with the blanks in biological knowledge, dissatisfied with the failures that still occur in medicine, displeased if the principles of scholarship, which are essential to staying abreast of change in the years after medical school, are neglected. Dean Chalmers effectively strengthened the school's commitment to continuous education, repeatedly emphasizing the forty years of learning that are required rather than merely the conventional four. He has stressed some of the changes of the past forty years, including for example the introduction of antibiotics and of anticancer drugs, organ transplantation and other surgical wizardry, immunization against viral diseases, synthetic hormones, a revolution in imaging the body, and the magnificent vistas of the intracellular universe that molecular biology has shown us, a wondrous

Thomas C. Chalmers, M.D.

firmanent within, leading the way to genetic engineering.

Dean Chalmers has schooled us all, faculty and students alike, to think critically. He wanted no Mount Sinai graduate to resemble Sganarelle, the hapless woodsman in Moliere's play, cudgeled into pretending to be a doctor in spite of himself. He bumbled into a few errors in explaining to a distraught father the pathogenesis of his daughter's illness. The father respectfully commented: "I am sure no one could present the case better. There is just one thing that bothers me. It seems to me you locate the organs incorrectly. The heart is on the left side, and the liver is on the right." The woodsman doctor, without missing a stroke, said, "Yes, in the old days that was so, but we have changed all that, and we now practice medicine by an entirely new method." I suspect that Dean Chalmers would like us to keep the best of the old information, as we learn about new developments in a forty-year personal curriculum of learning that is the professional life of a new physician.

Dean Chalmers has served in his office for ten of the school's fourteen years. During his tenure, counting today's happily assembled throng, 1,008 new physicians have joined our ranks, 87% of all those who hold the Mount Sinai diploma. Each of them has been taught how to apply the scientific method to man, all the while respecting the dignity of the individual, of his family, and of his culture. These two essential ways of thinking, scientific and humanistic, are the most precious attributes of a physician, more important than a mountain of unrelated facts which will become progressively more eroded each year.

Thomas C. Chalmers is a sovereign example of the worthy physician, part scientist, part humanist. A cultured man with a sense of purpose to his own life and a sense of reverence for the life of others; a diligent student and an indefatigable teacher. The good he has done will endure, as the Medical Center, including the School and Hospital, goes forward to a brighter future because of his tenure.

Dr. Chalmers, the Faculty of the Mount Sinai School of Medicine thank you for ten years of selfless devotion as dean, an office that you have distinguished by your integrity and by your accomplishments.

James F. Holland, M.D.
3 June 1983

Faculty Citation Honoring Thomas C. Chalmers

Thomas Clark Chalmers. As President of The Mount Sinai Medical Center and Dean of the Mount Sinai School of Medicine, of The City University of New York, you have guided the institution with firmness, grace and good humor through some of the most challenging years in medical history.

We honor you not only for the originality and loyalty that have characterized your leadership, but also for the honesty, faithfulness and refusal to compromise on those standards which distinguish you as a human being.

We honor you as a model teacher whose effectiveness is best gauged by the extraordinary productivity of your students. We honor you as a researcher, a recognized world leader both in the exploration of liver disease and in the vigorous and objective evaluation of clinical techniques.

Your zeal for medical science has always grown naturally from your love for people. You have never forgotten that the patient is not a disease but a person. Your concern for the quality of later life has brought us the nation's first Department of Geriatrics. Your concern for all human life has educated us to the horrors of nuclear war. In deep gratitude for your allegiance and true devotion to Mount Sinai, we the Faculty hereby confer upon you this citation of honor, the third day of June, 1983.

Introduction to James F. Glenn, MD

On June 1, 1983, James F. Glenn, MD, formally assumed the leadership of The Mount Sinai Medical Center, becoming the first person to serve as both president and chief executive officer. On July 1, he also became acting dean of the Mount Sinai School of Medicine, a position he will hold until a full-time dean is recruited during the coming year. Dr. Glenn succeeds Thomas C. Chalmers, MD, both as president and dean of the medical school. During an interview shortly after taking office, Dr. Glenn discussed his preliminary plans as president, and praised the leadership of his predecessor.

"I'm very glad that Dr. Chalmers will be with us in the future as Distinguished Service Professor," said Dr. Glenn. "We'll miss him during the coming year when he's on sabbatical, but I know he'll be available even then as we need his advice. He is totally dedicated to this institution, and he is very sensitive to the needs of others. I think he is a superb human being. He is a good and careful physician as well as a sensitive leader, and I think the institution could not have chosen better a decade ago when it selected him as President and Dean."

Following Dr. Chalmers' 10 years of leadership, Dr. Glenn faces the task of continuing Mount Sinai's steady improvement and of establishing his own style of leadership. He brings to the job a strong background in both medicine and medical administration. Alfred Stern, chairman of the Board of Trustees, praises Dr. Glenn's ability and character, and welcomes his arrival during this crucial phase in the development of Mount Sinai.

"Major medical centers are entering a new era, characterized by cuts in government support for research, the prospect of competitive reimbursement and new federal and local regulations," said Mr. Stern. "As a nationally respected clinician and academician and an accomplished manager, Dr. Glenn is powerfully equipped to meet these challenges at Mount Sinai."

Since 1980, Dr. Glenn has served as dean of the Emory University Medical School, where he was also professor of surgery (urology). During his tenure, he recruited five outstanding department chairmen to lead research programs, expanded the number of faculty members, and increased financial support from both public and private sources.

James F. Glenn, M.D.

Prior to 1980, he was chief of the Division of Urology at Duke University Medical Center, where he headed one of the largest and most prestigious urological residency programs in the country.

He has served as president of a number of respected medical societies, including the Society of Pediatric Urology, the Society of University Urologists, the Society of Pelvic Surgeons, and the Southeastern Section of the American Urological Association. His textbook, *Urologic Surgery*, is the standard reference text in the field.

Dr. Glenn said upon his arrival at Mount Sinai that one of the reasons he was attracted to the job was the long-time "excellence of the medical center as it exists today." As he plans toward the continued improvement of the center, his first task is to recruit a new dean for the medical school. To this end he has already appointed a search committee that represents the trustees, department chairmen, students, administration, and other constituencies. "The dean must," he said, "in our scheme of things, be a strong individual. He or she will be responsible for the medical school, and consequently must have the authority to run it."

Dr. Glenn's second priority is to continue the planning of the new hospital facilities. "I think that the planning process to date has been exquisitely developed by Mr. [Samuel] Davis, [executive vice president of the medical center]. It is clear that both new construction and renovation are required. The planning team, consisting of faculty, administration, and consultants, has developed a series of proposals, all of which have both merits and disadvantages. Through a careful process of evaluation, we are working out one specific generic plan which should carry the total development process well into the next century.

"One part of our plan is a new clinic, which will probably be the first private practice facility in New York for full-time faculty. This is important for a number of reasons. It has been the objective for some time to establish a physical presence for this group, and to give patients easier access to their doctors. Also, if we're going to rebuild, we must be able to relocate beds during the building period, and this move will facilitate the relocation exercise. Finally, an identifiable location should make it easier for Mount Sinai to attract new patients from a distance, both from this country and abroad."

While the rebuilding program proceeds in the hospital, Dr. Glenn foresees more gradual changes in the medical school. One of those changes, he predicts, will concern the way research is financed.

"I think all observers of the politics of medicine acknowledge that the growth of public funds for medical research has come to an end. Recognizing that, I think it is imperative that medical schools and research programs affiliate themselves with industry in ways that will be mutually beneficial. I anticipate that one of the major issues we will have to face in the next decade is the development of an ethical code of cooperation between academic institutions and commercial enterprise."

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The Mount Sinai Journal of Medicine
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Physiopathogenic Basis of Alcoholic Pancreatitis: The Effects of Elevated Cholinergic Tone and Increased "Pancreon" Ecbolic Response to CCK-PZ

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Abstract

Alcoholism initially elevates intrapancreatic cholinergic tone and increases acinar sensitivity to CCK-PZ, which result in pancreatic hypersecretion. If the intoxication is of abrupt onset, high intensity, and short duration, it may trigger an episode of acute pancreatitis; if the physiologic alterations are slow, moderate in intensity, and persistent, the end result is chronic pancreatitis. The anatomophysiologic bases for these concepts are the complex excitatory and inhibitory neuro-endocrine controls of secretion by the "pancreon." Neural impulses coming from the hypothalamic-bulbar centers are integrated by the intrapancreatic ganglia and the "intermediate autonomic nervous brains": antral (AANB), duodenal (DANB), and celiac (CANB). The endocrine control is exerted through excitatory and inhibitory regulatory peptides. In general, during the nonalcoholic stage, ethanol activates the inhibition of pancreatic secretion by an unidentified mechanism (PP?, enkephalins?, somatostatin?). As chronic alcoholism advances, however, ethanol increases responsiveness to CCK-PZ and, simultaneously, by activating excitatory nervous pathways, establishes increased cholinergic tone leading to protein hypersecretion. Eliminating the activity of these autonomic pancreatic reflex centers by interference with enteropancreatic reflex arcs by duodenal bypass (gastrojejunostomy) or by pharmacologic inhibition of mucosal receptors (local duodenal anesthesia and specific anticholinergics) would make physiologic sense either in treating or preventing acute inflammatory episodes in the pancreas.

The aim of this study is to present the physiopathogenic basis of acute and chronic alcoholic pancreatitis.

Our hypothesis postulates that alcoholic pancreatitis is the result of an elevated intrapancreatic cholinergic tone and an increased "pancreon" ecbolic response to CCK-PZ.

Our basic concept is that the nervous control of the "pancreon," the anatomofunctional unit of the exocrine pancreas (1), is centered in the intrapancreatic ganglia (1–3). This small "autonomic nervous brain" is under the bombardment of positive and negative impulses which derive from "intermediate autonomic nervous brains": two located in the digestive tract, the antral (AANB) and the duodenal (DANB), and one extradigestive, the celiac ganglion (CANB). All these three autonomic centers are under the modulating influence of the hypothalamic bulbar centers. The activity of the intrapancreatic ganglia determines cholinergic tone (1–3), one of the main ecbolic stimuli to the acinar cells of the "pancreon." The other agent is CCK-PZ. This peptide exerts its effects directly on receptors of the acinar cells, partly through the activation of neural reflexes from the duodenal autonomic nervous brain (DANB) and partly by

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releasing acetylcholine at nerve terminals (4, 5). See Figs. 1–3.

In chronic alcohol intoxication these two ecbolic agents, cholinergic tone and CCK-PZ, suffer significant modifications. Our hypothesis is that excessive, supranormal ecbolic stimulation of the acinar cells, when it is initiated slowly but persistently by moderate increments, leads to chronic pancreatitis, and when it is initiated by abrupt, high-intensity, short increments it induces acute pancreatitis.

In order to understand how ethanol exerts its physiopathologic effects on exocrine pancreas, it is essential to understand the neuro-endocrine control of the gland. In both the neural and endocrine mechanisms, two components, a positive (stimulatory) and a negative (inhibitory), must be considered.

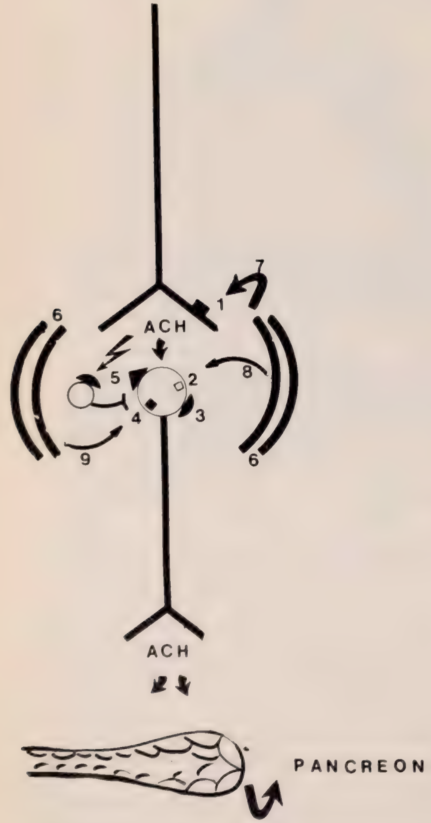

FIG. 1. Intrapancreatic ganglia: how cholinergic impulses are modulated by adrenergic fibers and interneuron. Peptidergic branch (neurons and fibers) of autonomic nervous system is not represented.

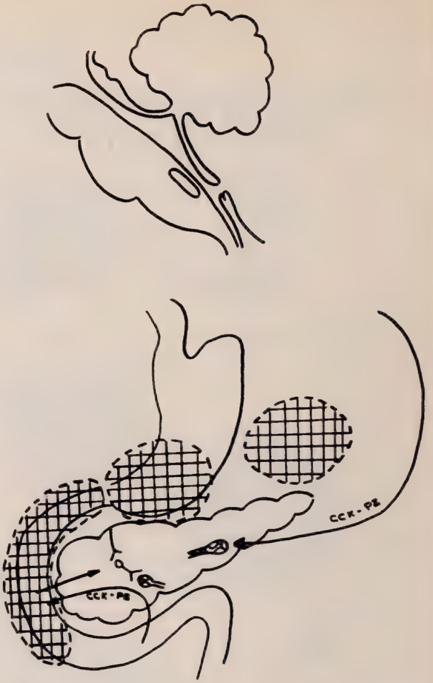

FIG. 2. The two main mechanisms by which CCK-PZ exerts ecbolic effects on the exocrine pancreas: (a) directly on acinar cells of the "pancreon"; (b) triggering neural reflexes from duodenal autonomic nervous brain.

Neural Control

The three major branches of the nervous system, the cholinergic, the adrenergic, and the peptidergic, may exert positive and negative influences on pancreon cells (1–102). A complex and delicate interaction occurs at the level of the intrapancreatic ganglia. The final result is what most authors have accepted as "cholinergic tone" (1–3, 93–98). One of the major changes induced by chronic alcoholism is increase of cholinergic tone, not only in the pancreas but in other organs, for example salivary glands, heart, adrenals, basal ganglia (103–105). See Fig. 4.

The intrapancreatic ganglia receive nervous impulses from the hypothalamic bulbar centers.

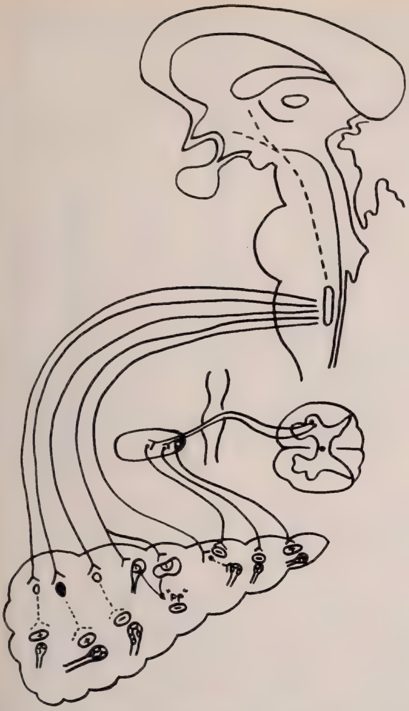

FIG. 3. Positive and negative influences on exocrine pancreas through cholinergic, peptidergic, and adrenergic branches of autonomic nervous system.

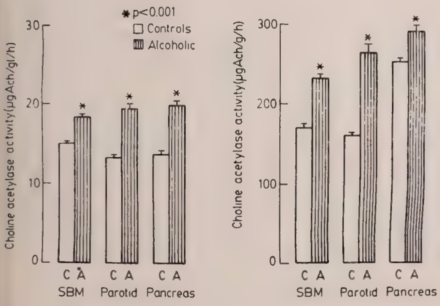

FIG. 4. Cholinacetylase activity (concentration to the left and total activity to the right) in submaxillary, parotid, and pancreatic gland before and after alcohol feeding; ethanol-induced significant increase in these three exocrine glands (see references 103–105).

These arrive at the pancreas in part directly in the cephalic phase (13–15, 30), but most impulses pass through the three intermediate autonomic nervous brains, the antral, the duodenal, and the celiac, where they participate in a complex integration process. The gastric phase in the neural control of exocrine pancreatic secretion depends upon impulses coming from the fundus (fundopancreatic reflexes) (6, 18, 38) and from the antrum (antropancreatic reflexes) (6, 18, 25, 26, 38, 51, 60, 106, 107). The latter are the most important. The antral stomach has a complex autonomic nervous brain (AANB). In addition to many nerve fibers that traverse it, the antrum has primary cholinergic and peptidergic neurones (12, 47, 62, 83, 88, 99, 108, 109). Its influences are exerted not only in the exocrine and endocrine pancreas but on the gallbladder and the gastric fundus (106, 107, 110, 111). See Fig. 5.

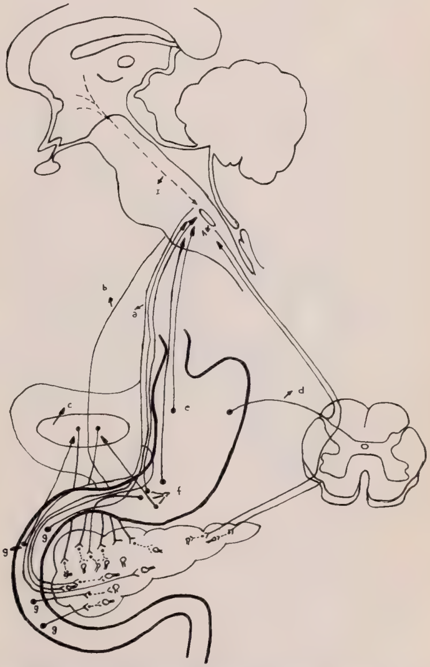

FIG. 5. Pathways of neural reflexes (cephalic, gastric, and intestinal) that normally influence exocrine pancreatic secretion: primary neurones in the gastric fundus (e), antrum (f) and the duodenum (g); participation of vagus nerves, spinal cord, and splanchnic nerves, and the integrative influence of the celiac plexus (c).

The duodenal autonomic nervous brain (DANB), upon which the intestinal phase of the nervous control of exocrine pancreatic secretion depends, is of great importance. Anatomically, it provides a rich macroscopic innervation of the duodenopancreas (1–3, 8–11, 92–98, 112). See Fig. 6. Many nerve fibers pass through it before entering the pancreas, mainly in the region between the pylorus and the papilla of Vater. The DANB contains, like the antrum, primary cholinergic and peptidergic neurons. Anatomic dissection reveals that the human pancreatic head has a richer innervation than the body and tail. This parallels the observation that choline acetylase activity is significantly greater in the head than in the body and tail of the gland (2, 3, 92, 94, 96–98, 103–105). See Fig. 7.

From a physiological point of view, the nervous impulses going from the DANB either to the intrapancreatic ganglia or directly to the pancreon cells are responsible for approximately 50% of the protein response in exocrine pancreatic secretion when one stimulates this trigger zone with fat or aminoacids. This is probably due to the fact that CCK-PZ and bombesin, released from the intestinal endocrine cells by these nutrients, exert part of their influence by triggering neural reflexes (4, 29, 67, 85, 86, 113–117).

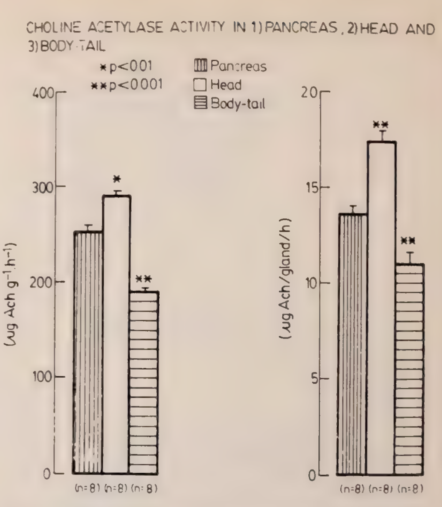

FIG. 7. Choline-acetylase activity (cholinergic tone) is significantly greater in head than in body and tail of gland (see references 103–105).

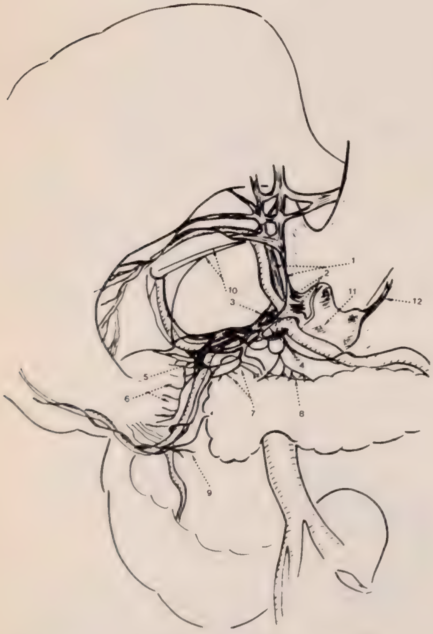

FIG. 6. Schematic drawing modeled from a human cadaver specimen demonstrating rich macroscopic innervation of duodenum and pancreas. Stomach has been turned to the right exposing its posterior surface. Vagus nerves (1), left celiac ganglia (11) and left splanchnic nerve (12), hepatic and gastroduodenal plexus sending branches to the pancreatic head (7,8), and duodenal bulb (5,6) are illustrated.

Experimental Evidence. That nervous impulses originating in the DANB participate in the control of exocrine pancreatic secretion and pancreatic duct pressure is clearly shown by two types of experiments. The first, performed in dogs (93, 94) secreting in response to secretin infusion, studied pancreatic secretion following application of lidocaine to the papilla (Fig. 8). These tests showed a marked fall of all pancreatic juice parameters, a finding that was confirmed by Konturek (20). The findings were interpreted as due to depression of the intrapancreatic cholinergic tone as a result of the interruption of nervous impulses going from the DANB to the pancreas. The second type of experiment was also done in dogs (52, 53). In these studies topical anesthesia of the DANB induced a 35% decrease of intrapancreatic ductal pressure. Furthermore, faradic stimulation of the DANB raised the pancreatic ductal pressure by 60% in an animal previously denervated by bilateral cervical truncal vagotomy and celiac plexus resection. On the other

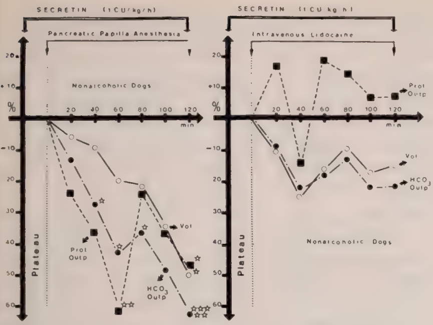

FIG. 8. Topical anesthesia of the pancreatic papilla (left) superimposed on a continuous perfusion of secretin induces significant fall of pancreatic secretion by interruption of duodeno-pancreatic reflexes with resultant decline of intrapancreatic cholinergic tone. Effects on EPS are not due to previous absorption into the bloodstream, as shown by tests carried out with the same protocol but with lidocaine infused intravenously (see references 93, 94).

hand, the intraduodenal infusion of 30% ethanol activated the inhibitory impulses from the DANB, inducing a decrease in pancreatic duct pressure of 50%. After vagal denervation, the administration of ethanol into the duodenum did not alter the duct pressure values.

These anatomical and functional studies lead to the conclusion that the DANB exerts its control on the exocrine pancreas by means of short, medium, and long reflexes (1–3, 94). See Fig. 9. The data from studies of pancreatic exocrine secretion reported by Harper (18, 38–41), White et al (6, 7), Debas et al (25–27, 110), and Schoon et al (106, 107) lead to a similar conclusion for the "antral autonomic nervous brain" (AANB): the antral brain exerts its effects on the exocrine pancreas by means of short, medium, and long reflexes. Furthermore, recent studies analyzing pancreatic duct pressure (52, 53) have revealed that intragastric administration of 30% ethanol, contrary to its effect in the duodenum, elicited an increase of pancreatic duct pressure which was not observed after cervical vagal transection. These studies demonstrate the crucial participation of the vagus and celiac ganglia in the control of intraductal pressure and exocrine pancreatic secretion. Indeed, acute bilateral cervical vagotomy induced a 45% fall of the resting pressure. Removal of the celiac ganglia resulted in a greater pressure decrease, a 70% fall. Complete vagal section decreased the rate of secretion in the secretin-stimulated pancreas.

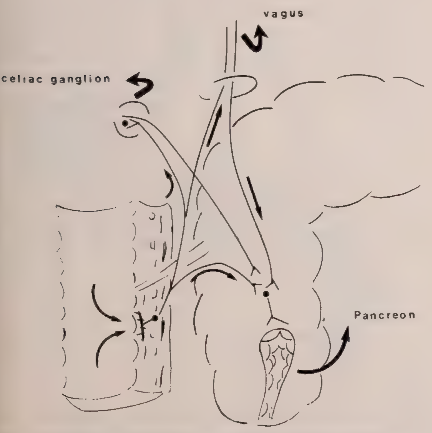

FIG. 9. Pathways of the duodeno-pancreatic reflexes: short, medium and long (see references 92–94).

Endocrine Control

Regulatory peptides acting on the pancreon's acinar cells with a positive and a negative effect can be distinguished. The mechanisms involved may be: endocrine, paracrine, neuro-endocrine, neuro-paracrine, and paracrine-neural. Among those with a mainly positive influence are members of the secretin and CCK-PZ family (31, 33, 45, 46, 59, 67, 90, 102, 118–132). Among those with a negative action on exocrine pancreatic secretion, all probably participating in the physiopathogenic changes induced by alcoholism, are pancreatic polypeptide (61, 68, 113, 134, 137, 138, 140, 143, 145, 146), enkephalins (24, 36, 55–57, 141), substance P (58), somatostatin (55, 100, 136), the anti-CCK-PZ of Caroli (63, 64), pancreotone (37, 39, 40), glucagon-entero-glucagon (139, 142, 144, 147), serotonin (19), TRH (34, 135), and ACTH (35).

In this analysis of the endocrine control of exocrine pancreatic secretion, the CCK-PZ effects on the exocrine pancreas should be clarified.

This peptide is the main ecbolic hormone of the pancreon. Fat and amino acids are its main releasers from the duodenum-jejunum. The release of CCK-PZ as well as secretin from the endocrine cells of the intestine is cholinergic-independent. This finding of Chey et al (119) and of others (4, 84–86, 113–117) indicates that the depression of exocrine pancreatic secretion following atropine or vagotomy is not the result of reduced cholinergic tone at the mucosa level, a concept of great importance in the interpretation of the effects of ethanol on the pancreas.

The second physiologic action of CCK-PZ that merits emphasis is that part of its effects on acinar cells are exerted through an indirect mechanism. Indeed, Grossman (4) stated CCK-PZ triggers a neural reflex from the duodenal autonomic nervous brain (DANB) by way of a paracrine-neural mechanism.

The third physiologic effect of this peptide is that its action on acinar cells is potentiated by a raised intrapancreatic cholinergic tone (60, 148–151) and that decreases in pancreatic polypeptide, a potent anti-CCK-PZ factor, facilitates CCK-PZ's ecbolic effects. Moreover, the release of PP, which is cholinergic-dependent, is also induced by CCK-PZ itself. This latter activity represents a feedback mechanism to restrain the effects of the hormone on its targets and, thus, to prevent unnecessary and dangerously excessive, supranormal stimulation of exocrine pancreatic secretion, gallbladder contraction, and intestinal motility.

The Effects of Ethanol on Exocrine Pancreas

The effects of alcohol on the pancreas are different in the nonalcoholic stage and during the alcohol-fed period.

Nonalcoholic Period

The initial investigations attempting to elucidate the effects of ethanol on exocrine pancreatic secretion (EPS) were performed with the bias of anticipating an excitatory response. This concept was disproved for humans by Dreiling et al (152) and by Valenzuela et al (153). Further studies indicated that intravenous ethanol, superimposed on continuous perfusion of secretin alone, secretin plus CCK-PZ, or secretin plus gastrin, either in humans or experimental animals (154–158), inhibited pancreatic exocrine secretion. The metabolite of alcohol, acetaldehyde (159, 160), did not.

Orrego Matte et al (161), working with the in vitro rat pancreas, suggested that ethanol interfered with a cholinergic mechanism. Further reports demonstrated that, in dogs and humans, the inhibitory effect of ethanol on EPS was prevented by truncal vagotomy (162), a ganglionic blocking agent (penthonium) (162), a blocker of muscarinic receptors (atropine) (155), and a synthetic anticholinergic (163), but not by reserpine-induced catecholamine depletion (176). These observations suggested that ethanol triggers inhibitory impulses in the central nervous system, which pass through a ganglionic synapse via nicotinic receptors and exert their effects on muscarinic receptors in the pancreatic polypeptide cells, which elaborate a strong and well-identified inhibitory peptide of EPS, cholinergic dependent and released by ethanol (148–151). Thus, intravenous ethanol, during the nonalcoholic stage, exerts its effect primarily on the central nervous system (hypothalamic bulbar centers) and activates the negative component of the pancreon neuro-endocrine control.

Under specific circumstances alcohol can excite pancreatic secretion, for instance in very low dosage intravenous infusions (164). See Figs. 10–12. Infusions of ethanol restricted to the stomach in the dog (165) and rat (166) also trigger excitation of exocrine pancreatic secretion. This had been attributed to gastrin release (167). However,

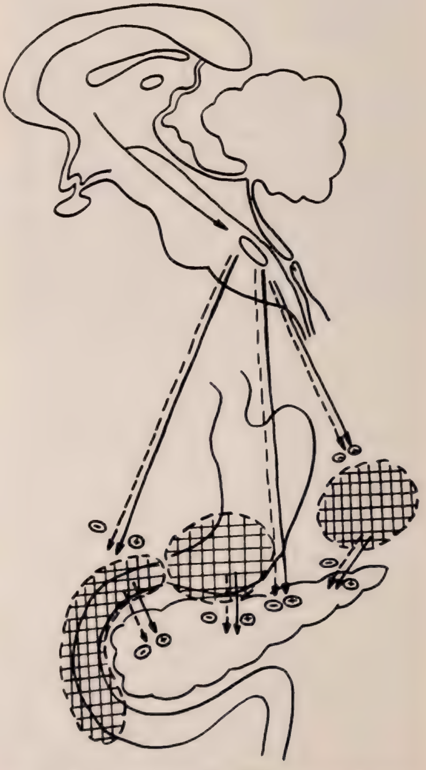

FIG. 10. Hypothalamic modulation of the intrapancreatic ganglia and intermediate autonomic nervous brains (antral, duodenal, and celiac), which exert positive and negative influences directly on pancreon units.

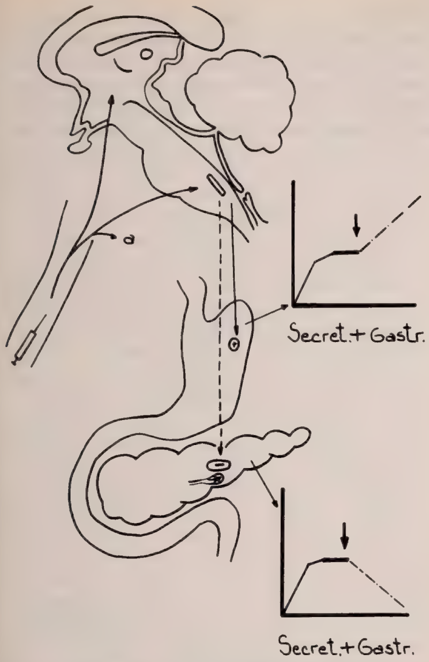

FIG. 11. Nonalcoholic stage: intravenous ethanol triggers excitatory response on gastric secretion and inhibition of pancreatic secretion.

recent data reporting changes in pancreatic duct pressures following intragastric alcohol (52, 53) suggest excitation by positive discharges from the antral autonomic nervous brain (AANB). These changes are prevented by previous acute bilateral transcervical vagotomy (Fig. 13).

Ethanol infused into the duodenum, either in humans (168–170) or animals (171), has very mild secretory effects on EPS but induces a drop in duct pressures (52, 53), which is also prevented by previous transcervical vagotomy. These data reinforce the evidence that alcohol during the nonalcoholic stage activates predominantly the negative component of the neuro-endocrine control of EPS from the duodenal autonomic nervous brain (Fig. 13). Furthermore, when ethanol is infused into the stomach in conjunction with a test meal, an inhibitory effect on EPS is noted (166, 172, 173). The same finding is observed after three months of alcohol feeding in dogs (173).

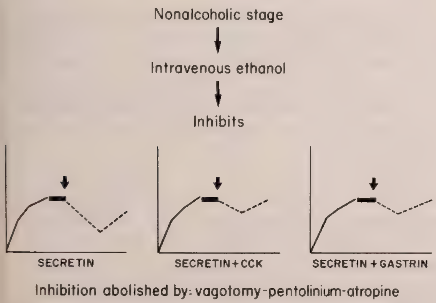

FIG. 12. Abolition of alcohol-induced inhibition of EPS in nonalcoholic stage by vagisection, pentolinium, and atropine.

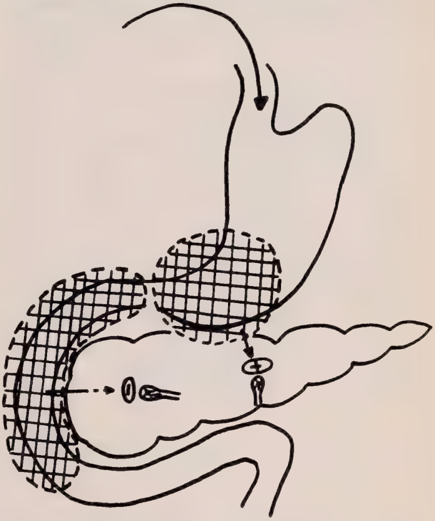

FIG. 13. In nonalcoholic stage, intragastric ethanol activates predominantly positive impulses from the antral and inhibitory influences from the duodenal autonomic nervous system.

Contrary to its effects on exocrine pancreatic secretion, intravenous ethanol, during the nonalcoholic stage, induces an excitatory response on gastric secretion (174–176). Increased motility of the sphincter of Oddi results when ethanol is given by the intravenous route or by intragastric injection (177, 178). This motor effect originates in the central nervous system and is abolished by previous vagotomy and hexamethonium (179–181).

The data that intravenous alcohol in the nonalcoholic stimulates gastric secretion and inhibits pancreatic secretion lends further support to the hypothesis of central nervous system action. The same effects, that is, gastric excitation, pancreatic inhibition, are observed following the exogenous administration of enkephalins (55–57). Finally, intravenous ethanol elevated plasma endorphin levels, an effect blocked by naloxone (182).

Alcohol-Fed Period

During the alcohol-fed stage, physiological changes develop in the neuro-endocrine control of EPS. In general, these changes can be summarized by the rule that sequentially there is a progressive loss of the negative component and a reciprocal prevalence of the positive one (Fig. 14). The major and crucial change, thus, is the reversal of an inhibitory response to an excitatory one (183–185) that can be blocked by atropine but not by a ganglionic blocking agent or vagotomy (186). Intravenous alcohol can also be observed to excite gastric secretion (175). These findings imply that intravenous alcohol, in the alcohol-fed animals, exerts its effects directly on the peripheral neurones, activiting muscarinic receptors and releasing acetylcholine at nerve terminals (175). Indeed, after truncal vagotomy, these neural effects are markedly potentiated (174, 175, 187). The same phenomenon occurs at pancreon level; that is, in vagotomized animals, chronic alcohol feeding induces a marked and significant augmentation of all pancreatic secretory parameters, especially total proteins and lipase activity (Fig. 15).

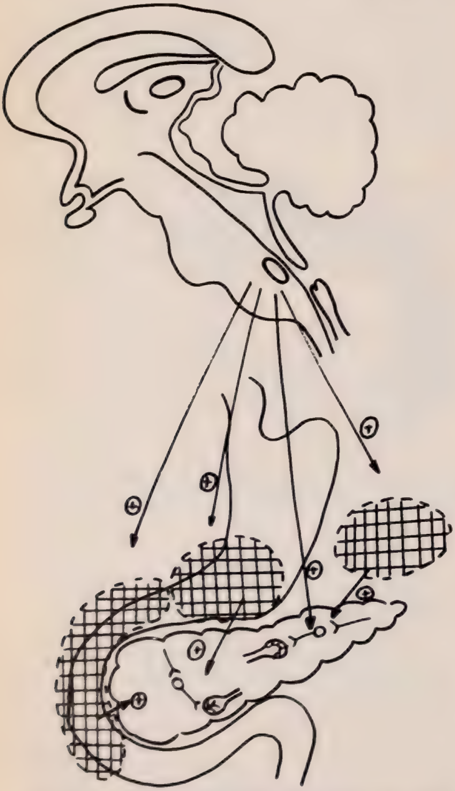

FIG. 14. As chronic alcoholic intoxication advances, there is progressive loss of inhibitory influences from hypothalamic-bulbar centers on intermediate autonomic nervous brains and on intrapancreatic ganglia; decentralization leads to hyperactivity of antral and duodenal centers.

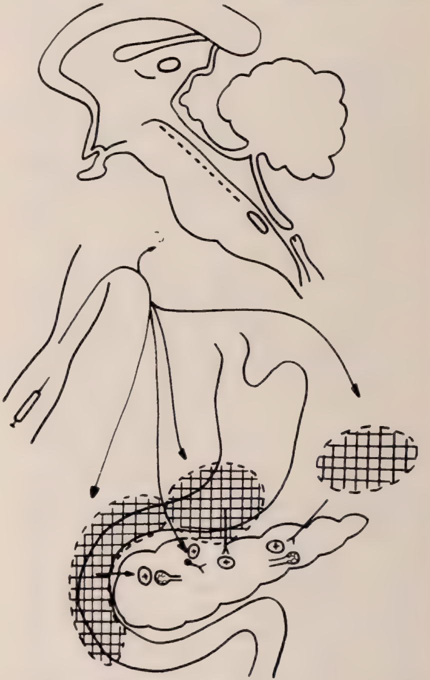

FIG. 15. In alcohol-treated period, intravenous ethanol elicits stimulation of EPS.

The data indicate that the peripheral neurones activated by ethanol are those of the intrapancreatic ganglia and the three intermediate autonomic nervous brains (antral, duodenal, and celiac). The result is an elevation of the intrapancreatic cholinergic tone (103–105, 188), which alters the inhibition of EPS to an excitatory response due to progressive loss of the negative component of the neuro-endocrine control of EPS (134, 140, 145, 146, 148, 149–151, 189). That ethanol intoxication is able to induce autonomic neuropathy has been shown in humans (190). The negative component most probably impaired during chronic alcoholic intoxication is the regulatory peptide PP since in dogs (151), as chronic alcoholism advances, CCK-PZ progressively loses its capacity to release this inhibitory factor. Other inhibitory peptides that may be involved are enkephalins, substance P, and somatostatin.

In summary: chronic ethanol intoxication, by blocking autonomic inhibitory reflexes, induces decentralization of the intermediate autonomic nervous brains and of the intrapancreatic ganglia. The neurones located in these centers, mainly in the antral autonomic nervous brain and the duodenal autonomic nervous brain, become hypersensitive to the usual endogenous stimulants (bowel distention, osmolarity increases) and to ethanol itself. The same mechanism develops at gastric level (191). As a consequence of increased activity of these autonomic nervous brains, increased cholinergic tone is induced in the pancreas, particularly in the head of the gland (1–3, 92–98, 103–105, 112).

Other physiologic findings which support these nervous mechanisms are those obtained by stimulation of the duodenal autonomic nervous brain. Indeed, oleic acid infused into the duodenum, when superimposed on a continuous perfusion of secretin (192), produces a significant increase in protein secretion (Fig. 16). After 4 months of alcohol feeding, intraduodenal oleic acid induces increased protein output 600% higher than that obtained in control animals. At 24 months and 36 months of alcohol feeding, these percentages diminish slightly. Hydrelatic responses, however, continue to increase (Fig. 17). In the alcoholic dog (193), atropinization markedly inhibits the secretory response to intraduodenal oleic acid and abolishes the difference between control and alcohol-fed animals (Fig. 18). Since neither atropine nor vagotomy influences the plasma levels of secretin and CCK-PZ (85, 86, 113–119), and fat and amino acids stimulate secretion via neural reflexes (4, 85, 86, 115–117), the data indicate that activity of the duodenal autonomic nervous brain results in hyperactivity of cholinergic neurones through normal pathways, that is, activation of the nicotinic receptors and release of acetylcholine at nerve terminals. This hyperactivity also augments the responses to the usual endog-

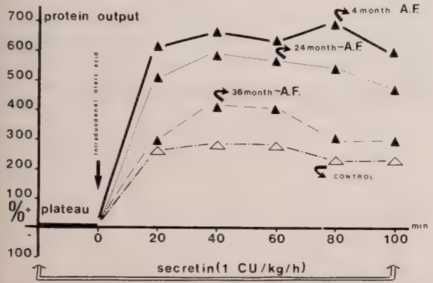

FIG. 16. Protein hypersecretion following intraduodenal oleic acid instillation at sequential periods of alcohol feeding in canines.

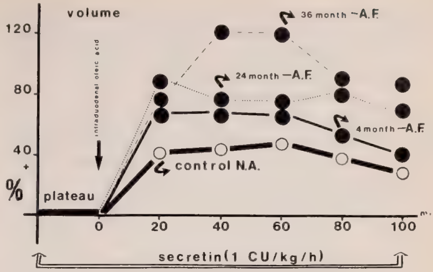

FIG. 17. Continuous increase in hydrelatic EPS response to intraduodenal oleic acid as alcohol intoxication progresses, consistent with histopathologic finding of hyperplastic ductular mass.

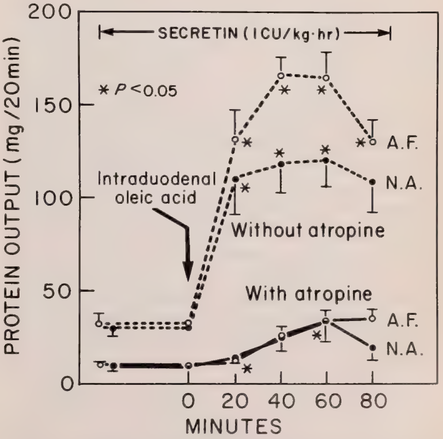

FIG. 18. Atropinization of the animal diminishes intraduodenal-oleic-acid-induced EPS response and abolishes percentage differences in plateau levels between alcohol-fed and control dogs (see reference 193).

enous stimulants (distention, osmolarity, activation of neuronal muscarinic receptors by CCK-PZ and other peptides such as gastrin, bombesin) all of which release acetylcholine at nerve terminals.

To recapitulate, gastrin and CCK-PZ (5), nervous decentralization (99), reserpine (194), and the anticholinesterase effects of ethanol (5, 195) induce a potentiation of secretion via this pathway (Fig. 19).

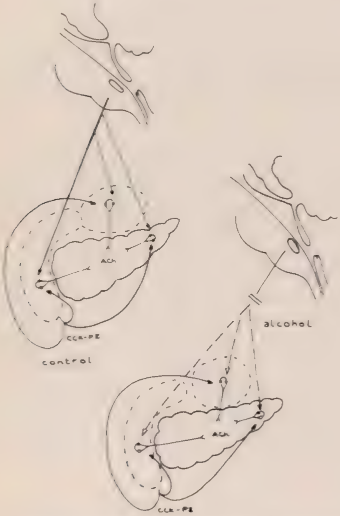

FIG. 19. CCK-PZ-elicited neural reflexes via muscarinic pathways; this reflex pathway is potentiated by chronic alcoholism.

Another mechanism contributing to the neural reflexes is the augmented pancreon ecbolic response to CCK-PZ facilitated or potentiated by two factors: (a) the high intrapancreatic cholinergic tone (60) and (b) diminished release of anti-CCK-PZ factors such as PP (151). The increased pancreon ecbolic response to CCK-PZ administered intravenously during the alcohol-fed stage is neatly demonstrated by several studies in experimental animals and in humans. In dogs in the chronic alcoholic stage, the protein output plateau is 100% higher than that observed in the nonalcoholic period (183, 184). Other examples of pancreon overresponsiveness to intravenous CCK-PZ induced by chronic alcoholism are the results obtained in dogs following topical duodenal papilla anesthesia and following intravenous infusion of lidocaine alone, as well as those associated with atropine administration superimposed on continuous perfusion of secretin plus CCK-PZ (93). See Figs. 20, 21. Indeed, these data demonstrate that topical or intravenous lidocaine potentiated by atropine blocks the release of an anti-CCK-PZ factor. In both the control and alcohol-fed animals, volume and protein output are significantly augmented, but in the chronic alcoholic animals the percentage changes are greater (93). See Fig. 21. Intravenous lidocaine and atropine, perfused together, gave a greater potentiation effect because the former blocks nicotinic receptors and the latter blocks muscarinic receptors; both participate in the release of the anti-CCK-PZ factor, PP. The blockade of the anti-CCK-PZ factor also facilitates secretin-induced ecbolic activity. There is good evidence in dogs of an ethanol induction of secretin receptors in the pancreon acinar cells (148). Consistent with these findings are the studies of Renner et al (196) in humans. Collecting pure pancreatic juice from the main pancreatic duct endoscopically, these investigators showed that a single bolus intravenous injection of CCK-PZ, but not secretin, produced an enzyme response significantly greater in chronic alcoholics than in nonalcoholic subjects. Brugge et al (197) and others (158, 198–207) have reported increased basal protein secretion in alcoholic humans, dogs, and rats.

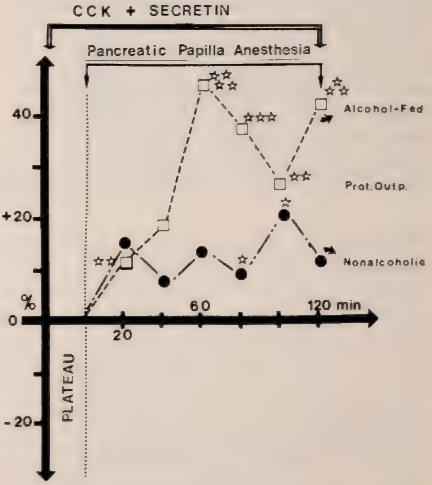

FIG. 20. Topical lidocaine anesthesia of pancreatic papilla in dog subjected to continuous perfusion of secretin plus CCK-PZ induces a greater percentage EPS response in alcohol-treated dogs than in controls (see reference 93).

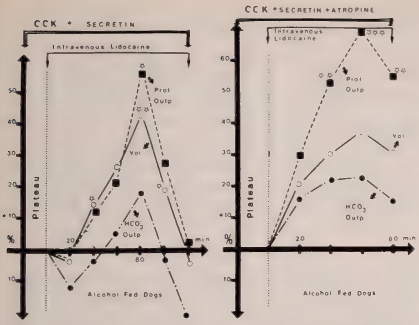

FIG. 21. Intravenous lidocaine induces greater EPS protein response in alcohol-fed dogs than in controls; this phenomenon is potentiated by adding atropine (see reference 93).

Hypersecretion of protein can be observed in other conditions, for example following intraduodenal mannitol, following intravenous CCK-PZ perfusion, in severe chronic renal failure in humans (208), in pregnant dogs (209, 210), and following induced hypercalcemia. Furthermore, Noel-Jorand et al (213) have shown that calcium-treated dogs stimulated by graded doses of either cerulein or urecholine display increases in the sensitivity of acinar cells to these two agents. These findings could explain the occurrence of ductal proteinacious plugs in calcium-treated dogs as well as in humans with parathyroidism. Furthermore, prolonged steroid administration in humans and in experimental animals (214) also triggers excessive, supranormal EPS ecbolic responses. Finally, a recent report (215) suggests that cystic fibrosis may be preceded by a stage of EPS hyperfunction.

Wormsley (216) and Gaia et al (217) have shown that in humans, rates of protein synthesis, analyzed by the incorporation of ^{75}Se-methionine into pancreatic exocrine proteins, are significantly greater in the presence of chronic pancreatitis. In these persons, the relative rate of incorporation of ^{75}Se-methionine into secreted proteins is more rapid than normal, so that they secrete into the duodenum an increased ratio of labeled-to-unlabeled proteins (216). This implies that the rate of synthesis is increased in surviving acinar cells (218). These findings correlate with the ultrastructural changes detected in the acinar cells of patients with chronic pancreatitis (219). Indeed, surviving cells undergo hypertrophy and increased nuclear and nucleolar size, as well as increases in the rough endoplasmic reticulum, the Golgi apparatus, and the number of prozymogen granules, changes that have been interpreted as indicating compensatory hypertrophy to produce greater enzyme synthesizing capacity.

Summary

To recapitulate, it is clear that chronic alcoholism as well as other clinical situations such as chronic renal failure (208, 220), cystic fibrosis (215), pregnancy (209, 210), prolonged corticotherapy (214), and hypercalcemia (211–213) are associated with supranormal pancreon ecbolic stimulation. This state of protein hypersecretion, when induced by slow and progressive development, would result in acinar fat deposition (221–224) and then in cellular damage, either acinar atrophy, acinar dedifferentiation (pseudotubules), or acinar replacement by centro-acinar-ductal cells. Peri-acinar and periductal fibrosis would result from ethanol-induced increased intrapancreatic cholinergic tone (Celener et al, unpublished observations). The sprouting of new canaliculi from large and medium-sized ducts in the rat (Celener et al, unpublished observations) and the presence of greater numbers of binucleated cells in humans (219) are indicators of a regenerative effort by the pancreatic gland (225–227). This is not unexpected, since CCK-PZ is a major pancreatotrophic agent (121, 228, 229). Moreover, pancreatic ductal neogenesis was stressed by Dreiling (131, 230, 231) as one of the first changes induced by intoxication with ethanol and other noxious substances. This ductular reduplication is responsible for the increased flow rate and bicarbonate output of the pancreas, the initial secretory change in minimal pancreatic pathology in humans. Gregg and Sherma (232) have confirmed this hydrelatic hypersecretion in humans after secretin injection by collecting endoscopically pure pancreatic juice in the early stages of alcoholic chronic pancreatitis. On the other hand, these findings were not corroborated by Sahel and Sarles (199), either before or after secretin or CCK-PZ stimulation. Noel-Jorand et al (198) reported augmented basal protein concentration in the dog. Moreover, in the dog, dose-response curves to secretin have revealed a greater hydrelatic capacity of EPS after 6 months (148) as well as after 2 years of alcohol feeding (185).

Thus, it seems clear that protein plugs in chronic alcoholism and other conditions are another manifestation, at ductal lumen level, of excessive, supranormal ecbolic stimulation of the pancreon acinar cells. Although these plugs are not the pivotal factor that triggers the histopathogenesis of chronic pancreatitis, by obstructing ductules they can contribute to the aggravation or acceleration of disruption of the cellular organelles.

The stage of acinar hyperfunction, correlated as it is with hypertrophy and hyperplasia of the ductular mass, is associated with significant increase in the size and weight of the gland. This is easily demonstrated in humans by computerized tomography. In one alcoholic dog followed for 3 years, autopsy disclosed that the weight of the pancreatic gland was almost double the average for animals of the same body weight (202, 207) (Fig. 22).

When the chronic alcoholic suddenly drinks to excess or indulges in a copious meal rich in protein and fat, an excessive, supranormal pancreon ecbolic stimulation of abrupt onset, high intensity, and relatively short duration follows and may trigger disruption of the cellular organelles involved in protein synthesis, with a resultant extrusion of enzymes through the basolateral membranes of the acinar cells into the pancreas interstitium. This sequence can lead to an episode of acute pancreatitis, the first manifestation of subclinical chronic pancreatitis (233–237) in the alcoholic. Other instances in which sudden increase in cholinergic tone or markedly increased stimulation of the acini produce acute pancreatic inflammation include the presence of scorpion toxin (240–242) or cholinergic and anticholinesterase agents (243, 244) and supramaximal stimulation with CCK-PZ or cerulein (245, 246).

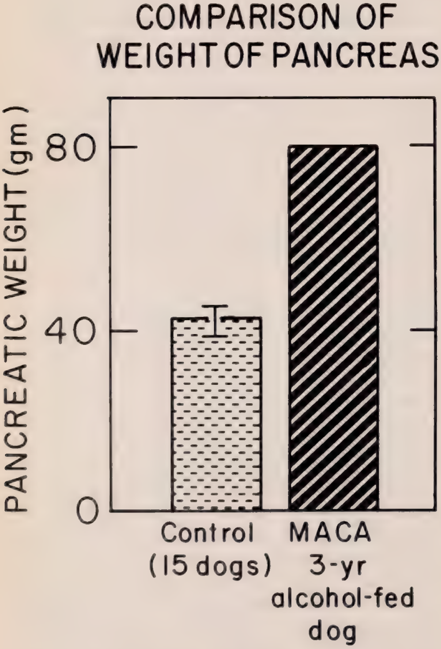

FIG. 22. Weight of pancreas before and 3 years after alcohol feeding. Control is average of 15 dogs of weight equivalent to alcohol-fed animal at inception of study (see reference 202).

Clinical Applications

This physiologic discussion does have possible clinical applications. An inflamed organ heals best when placed at rest. The acutely inflamed pancreas, thus, can be rested by surgically shunting the antroduodenal zone or by pharmacologically diminishing bombardment of the intrapancreatic ganglia or the "pancreon" units themselves. The former approach was tried in the fifties by Richman et al (238–240). They treated with success three patients suffering from acute relapsing alcoholic pancreatitis with subtotal gastrectomy and Billroth II reconstruction. This procedure diminished pancreatic excitation normally arising in this anatomic zone. The pharmacologic approach to acute pancreatitis ought to be treatment of increased cholinergic tone or increased sensitivity of the acinar cells to CCK-PZ. While nasogastric suction by removing gastric acid can reduce the intensity of hormonal stimulation via the secretin mechanism (247), it has no value in the patient whose gastric contents are alkaline. Other measures would theoretically include:

1. avoidance of pancreatic stimulation by parenteral alimentation.
2. administration of muscarinic receptor blockers such as pirenzepine.
3. administration of CCK-PZ antagonists such as pancreatic polypeptide, substance P, or somatostatin.
4. blockade of the pancreatic secretory trigger zone, that is, the antral and duodenal autonomic nervous brains, by local perfusion with anesthetic agents such as lidocaine.

Some of these therapies have been tried, others are undergoing study, and the remainder await therapeutic evaluation.

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Submitted for publication March 1983.

The Mount Sinai Journal of Medicine
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Electrocardiographic Changes in Treatment of Uncomplicated Essential Hypertension

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Abstract

Over 400 cases of asymptomatic essential hypertension separated from secondary hypertension by routine testing were reviewed retrospectively. Patients with previous intermittent claudication, angina pectoris, stroke, transient ischemic attacks, overt myocardial infarction (MI), "silent" myocardial "necrosis" (9 cases), "overload" pattern (5 cases), accelerated hypertension, azotemia, or any overt manifestation of arteriosclerosis were excluded. Also excluded were patients with other major diseases such as diabetes mellitus, and patients with less than three years of therapy. This left 136 cases treated for 3–28 years, including 15 instances on ECG of asymptomatic, usually anterolateral myocardial damage ("necrosis") occurring while the patients were normotensive. Only one patient had a symptomatic transmural posterior wall infarction. If these "necroses" do indeed represent small infarctions, the nearly 100% incidence of "silence" in this group contrasts with the 20% incidence of such "silence" in all myocardial infarctions in the general population. No instance of stroke or renal insufficiency was observed in the defined group. There were 8 deaths, 5 noncardiac and 3 probably cardiac, but none were preceded by the ECG changes described in the 15 cases of "necrosis."

Although successful drug therapy for essential hypertension has decreased the incidence of stroke, renal failure, and malignant hypertension, a difference of opinion remains on the effect of drug therapy on the myocardium and especially on myocardial infarction (MI). In two studies (1, 2) no significant effect was found, whereas in one (3) the incidence was decreased. Most studies, however, have included patients with overt arteriosclerosis, myocardial infarction early in the course of treatment, or other associated diseases. It therefore became of interest to review treated patients who initially had no overt manifestations of arteriosclerosis, particularly since some of these patients developed electrocardiographic evidence of myocardial damage with possible "necrosis" while they were normotensive.

Materials and Methods

Over 400 cases were therefore reviewed retrospectively. When symptomatic myocardial infarction (MI) or stroke occurred, the patients most often had manifestations of associated arteriosclerosis. Some had prior overt MI or stroke, intermittent claudication, angina pectoris, transient ischemic cerebral attacks, bundle branch block, renal insufficiency, or some major associated disease such as diabetes mellitus, gout, or systemic sclerosis. Others developed overt MI only after short periods of treatment for hypertension. Two patients treated for less than 3 years had overt transmural MIs. All such cases, including those treated for less than 3 years, were therefore excluded. It was the purpose of the study to analyze the effect, particularly on the heart, of long term control of blood pressure in patients with no initial overt manifestations of associated arteriosclerosis.

In reviewing the remaining 151 asymptomatic cases seen over periods of from 3 to 28 years, 4 were found with the classical left ventricular "ov-

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erload" ECG patterns, which remained relatively unchanged when they became normotensive. One patient had left ventricular overload which improved with treatment. When normotensive under treatment he later developed myocardial damage or "necrosis" indistinguishable from an old "silent" MI. Nine other patients, when first seen, had electrocardiographic signs of predominantly anterolateral myocardial damage ("necrosis") which were asymptomatic. These were apparent by the presence of Q waves and inverted T's in leads 1, AVL, and V4, 5, or 6 and by evolution of the ECG changes with time. All these patients were therefore excluded from the study. Secondary hypertension due to pheochromocytoma, renovascular hypertension, aldosteronism, Cushing's syndrome, accelerated malignant hypertension, and renal insufficiency were also excluded by initial routine testing. Three patients had small strokes which never recurred, but they were also eliminated from the study.

There remained 136 essential hypertensive patients who had no symptomatic manifestations of arteriosclerosis and whose routine history, clinical examination, automated blood counts, blood chemistries and sedimentation rates, twelve-lead electrocardiograms, rapid sequence intravenous pyelograms (IVPs), and chest x-rays did not, as far as could be determined, reveal evidence of asymptomatic arteriosclerosis.

Mean systolic and diastolic pressures were determined, the latter from the fifth phase, and were measured in the standing and recumbent positions. These patients were seen every six weeks and were completely evaluated as outlined above, except for IVPs, every year or occasionally every two years. Blood pressure was usually brought under control (140/90 or less) within several months (Table I). Various drug regimens were used, including reserpine, diuretics, guanethidine, methyldopa, clonidine, prazosin, and alpha and beta adrenergic blockers.

Some patients had been treated by other physicians prior to these observations and some were eventually lost to follow-up because of change of address or physician. The results reported here, therefore, apply only to the time that these patients were under observation by the author.

TABLE I

Population Characteristics (Mean ± SE): 70 Men, 66 Women

Age at onset of observation	50 yrs. 1 mo. ± 1 yr. 2 mos.
Time of known hypertension prior to first observation	7 yrs. 6 mos. ± 8 mos.
Time of observation and treatment	9 yrs. 4 mos. ± 5 mos.
Status before treatment	
systolic blood pressure	185 ± 2 mm Hg
diastolic blood pressure	109 ± 1.4 mm Hg
Status at end of treatment	
systolic blood pressure	130 ± 1.4 mm Hg
diastolic blood pressure	79 ± 0.7 mm Hg

TABLE II

Electrocardiographic and Clinical Changes During Treatment

1. Left axis deviation		94
2. Improved QRS voltage and pattern		30
3. Nonspecific ECG changes before or during treatment		23
4. Myocardial damage or "necroses" ("silent" MI's?)		15
5. Overt MI		1
6. Angina pectoris		0
7. Atrial fibrillation		2
8. Intermittent claudication		2
9. Stroke		0
10. Renal insufficiency		0
11. Deaths		8
cardiac (unrelated to 3 or 4)	3	
noncardiac	5	

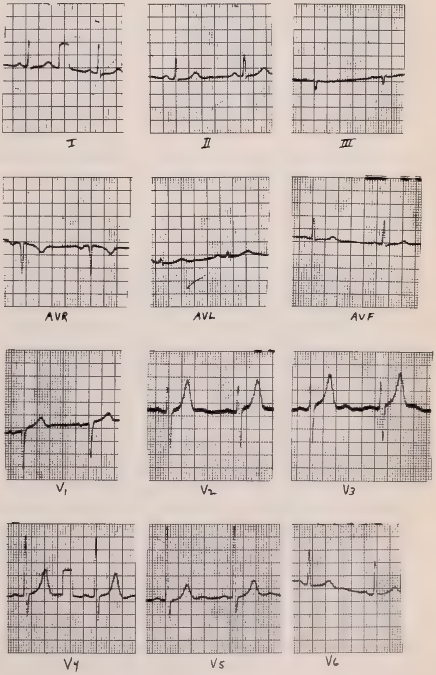

FIG. 1. ECG, 54-year-old man prior to treatment. BP: 220/120.

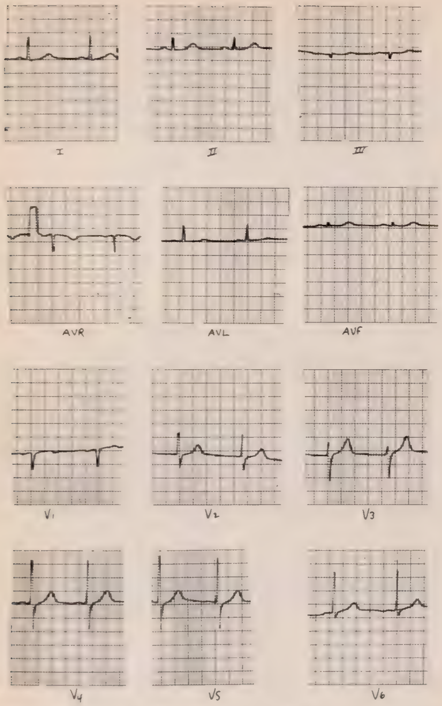

FIG. 2. ECG, same patient: improvement after 8 years of observation and treatment. BP: 130/80.

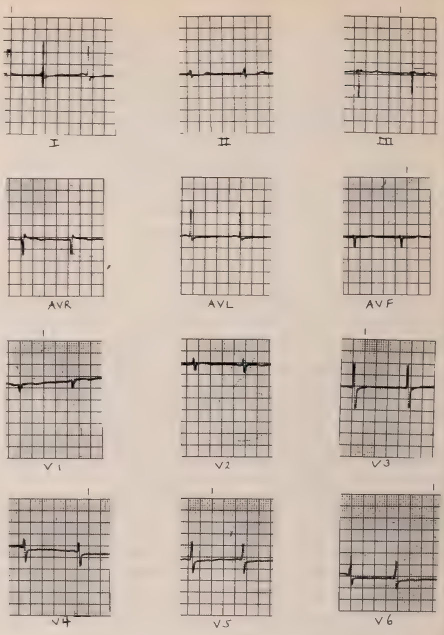

FIG. 3. ECG, 51-year-old woman before therapy: nonspecific changes. BP: 190/118.

Results

Electrocardiographically, of the 136 patients, 94 had left axis deviation (Table II). Only 30 cases had improved QRS and T wave voltage and pattern changes despite effective therapy (Figs. 1, 2). Either before or during therapy, 23 patients had nonspecific changes such as T1 lower than T3, slight increase in the QRS interval, or slight deviation of the ST segment (Fig. 3). While they were on therapy and hence normotensive, 15 patients with previously normal ECGs developed myocardial damage or "necrosis" manifested by Q waves and inverted T waves in lead 1, AVL, and V4, 5, and 6, or occasionally in only one or two of these last leads. These changes left variable residua (Figs. 4, 5). It would be difficult to maintain that these changes were due to "overload" since the patients were normotensive when surveyed. The exact time of the development of damage or "necrosis" could not be determined because it was asymptomatic and probably involved a small area. Moreover, the periodic surveys failed to reveal acute enzyme changes. The ECG changes therefore represented damage or "necroses" of indeterminate age in months.

Although on routine PA chest x-ray some of the cardiac silhouettes exhibited either a decrease or (occasionally) an increase in size, most remained unchanged. There was no correlation between any change in the cardiac silhouette and the electrocardiographic changes. There also seemed to be no apparent consistent relation between the type of drug therapy and the ECG changes. Age also did not appear to correlate with the ECG changes. The youngest patient with ECG signs of damage or "necrosis" was 35 years old and the oldest, 80. With a few exceptions the areas involved were anterolateral.

Only one patient in this group developed an overt uncomplicated posterior MI requiring hospitalization; he was obese and had a type A personality (4). He subsequently developed a bleeding duodenal ulcer and later died suddenly at the age of 64. Seven other patients died, one

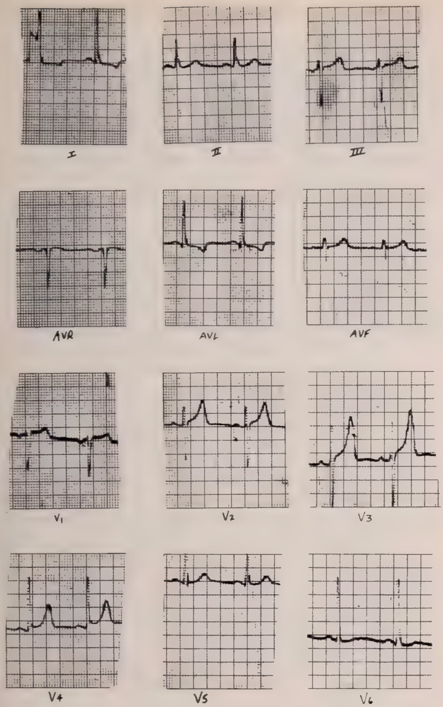

FIG. 4. ECG, 35-year-old woman 8 years after observation and treatment: recent anterolateral "necrosis." Initial ECG normal; initial BP 240/140; BP 8 years later: 110/70.

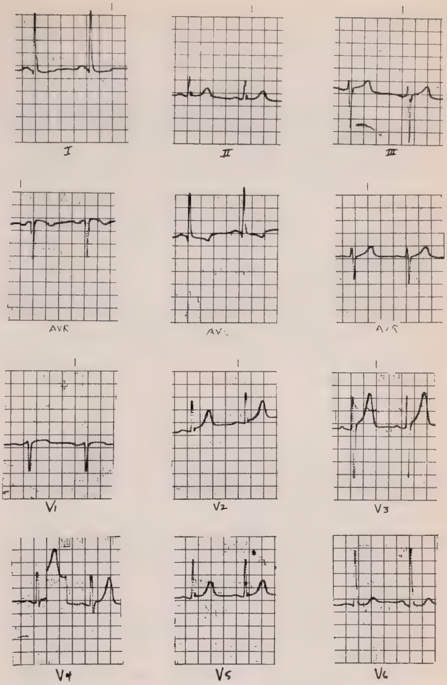

FIG. 5. ECG, same patient 4 years later: evolution of "necrosis." BP: 110/70.

at 70 years of age of a postoperative ruptured abdominal aneurysm; three at 60, 69, and 72 years of age of colonic carcinoma with metastases; one of acute myelogenous leukemia at 64 years; one with emphysema, heart block, and congestive heart failure at 72; and one with bilateral Paget's disease of the breast, postunilateral mastectomy, and ventricular extra systoles followed by sudden death at 81. None of these patients were among the 15 with myocardial damage or "necrosis."

No patient in the study group, including those with myocardial damage or "necrosis," had postinfarction angina pectoris, stroke, or renal insufficiency, but two patients not of that group developed intermittent claudication and two developed auricular fibrillation.

Discussion

Electrocardiographically, most ventricular hypertrophy of essential hypertension is associated with left axis deviation and is often diagnosed because of the clinical presence of essential hypertension. Left ventricular hypertrophy can sometimes (5) be distinguished by changed QRS pattern and increased QRS voltage measurements (6–8) and usually by echocardiography (9, 10), radionuclide testing (11), or change with treatment in the QRS voltage and distribution or in T3 orientation. In all but one of the cases reviewed, left ventricular "overload" was not reversed by treatment and remained relatively unchanged, and therefore probably represented left ventricular subendocardial "necrosis" (12, 13).

An attempt here was made to separate essential hypertensive patients with possible overt associated arteriosclerosis from those without overt arteriosclerosis who were under adequate medical therapy for at least three years. Such patients may develop electrocardiographic evidence of myocardial damage or "necrosis" before treatment is begun or even after blood pressure has been kept normal for years. Whether such "necroses" are due to "silent" myocardial infarctions or not can only be determined by echocardiographic, radionuclide, and other techniques. The incidence of "silent" MI's in the general population is only 20% (14), whereas, if these electrocardiographic indications of "necrosis" were proved to be evidence of "silent" MIs, the incidence of such "silence" in these patients could be nearly 100%. Other possibilities that must be considered are the effects of underperfusion of hypertrophied and hyperplastic myocardium, the absorption of hyperplastic myocardium because of the decrease in blood pressure, and, finally, the effect of the drugs themselves. Whether these ECG changes represent such factors or are evidence of "silent" MIs can only be determined by further research.

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Submitted for publication March 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Blood Transfusions and Kidney Transplantation: Review of Controversies

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Abstract

The entire field of renal transplant medicine was revolutionized in 1973 with the introduction of the concept that pretransplant blood transfusions improve the outcome of kidney grafts. This paper reviews some of the major topics of controversy presented in the myriad of articles since that time.

The beneficial role of pretransplant blood transfusions on kidney graft survival was observed by Opelz in 1973 in a retrospective study (1), but was initially controversial; blood transfusions in potential recipients of renal transplants had, for years, been deliberately avoided because of the fear of sensitization. Soon, however, a number of published studies, both retrospective (2, 3) and prospective (4), confirmed these 1973 findings. The concept of improved kidney graft survival by pretransplant blood transfusions is now generally accepted.

A retrospective study (2) of patients receiving transplants prior to 1976 in Lyon, France, reported one-year graft survival rates of 35% for nontransfused patients and 67% for patients receiving more than ten blood transfusions. Opelz and Terasaki (3) studied 1,360 cadaver-donor kidney transplants and, in 1978, reported one-year survival rates of 42% without transfusions and 71% with more than twenty transfusions. At four years, the survival rates were 30% without and 65% with transfusions.

Confirmation of retrospective results by a prospective study was reported by Sirchia et al in 1981 (4). A retrospective investigation of 319 cadaveric transplants had reported two-year survival rates of 47% in nontransfused and 64% in transfused recipients; as a result, a policy of giving potential recipients three units of packed RBCs at fifteen-day intervals began in 1978. The post-1978 prospective study confirmed the earlier results with a two-year survival rate of 50% in nontransfused and 65% in transfused recipients. One of the best graft survival results came from the Eurotransplant Foundation in The Netherlands, where Persijn et al (5) reported 87% one-year graft survival in thirty patients with one pretransplant transfusion, compared to one-year graft survival of 32% in seventy-four nontransfused patients.

With acceptance of the benefit of pretransplant blood transfusions on kidney graft survival, controversy arose over the dosage of transfusions, the blood product used, the time sequence of transfusion, the sensitization rate, the influence of HLA matching, and the mechanism of action.

Dosage. Opelz et al (6) found a stepwise increase in survival rates with increasing numbers of transfusions. In a study of 538 patients, survival rose from 38% in the nontransfused group to 50% in patients receiving one to five units, to 60% with six to twenty units, and to 72% in patients receiving more than twenty units of packed RBCs. Opelz and Terasaki had also previously shown in 1978 (3) that one transfusion did not have a statistically significant influence on graft outcome. In contrast to these results, a prospective study by Persijn et al (5) demonstrated that single-unit transfusion could lead to prolonged cadaveric kidney graft survival: nineteen patients who had one pretransplant transfusion of leukocyte-poor blood had a 79% graft survival rate at 240 days. The authors attributed the difference in results to the racial heterogeneity in

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other studies, but their small sample size could not be ruled out as the cause of unusual results. Fehrman et al (7), in Stockholm, studied 229 cadaveric renal grafts and found a better graft survival rate in patients receiving more than four units of transfusions compared to patients who had never received blood. However, there was no improved survival of grafts for those Swedish patients who had received one to three units of transfusions.

Blood Products. A variety of blood products have been used for pretransplant transfusions. Opelz and Terasaki (8) noted the ineffectiveness of frozen blood transfusions. In a study of single-unit transfusion with packed cells, whole blood, and frozen blood, only packed cells appeared to have a significant effect. This was confirmed by Spees et al (9), who found that packed RBCs, washed RBCs, and mixed varieties of blood products were more effective than frozen RBCs in achieving improved graft survival. A study from The Netherlands (5) revealed extremely poor survival of grafts in patients given one unit of leukocyte-free blood: the results were comparable to those of patients who did not receive any transfusions. This was in contrast to those patients who received a washed RBC (that is, leukocyte-poor) transfusion and who had a high one-year graft survival rate.

There was some attempt to decrease the risk of immunization by matching transfused blood for HLA A and B antigens. It was found that even with a good degree of HLA matching, the frequency of antibody production could not be significantly decreased. This suggested that the antigens were not as important as the patient's innate response to allogenic challenges. Of interest was the observation that matching for HLA antigens in transfusions produced poorer graft survival (10).

Timing. Persijn et al (5) could find no correlation between graft survival and timing of transfusions in either their retrospective or their prospective study groups. This was also the finding of the International Workshop Study (11). Although some authors (12) have reported improved graft survival when transfusion occurs within six months of the transplantation procedure, patients receiving multiple transfusions have usually received their last unit during that time period. Corry et al (13) also found no difference in graft survival between those patients who received and those patients who did not receive transfusions during the six months prior to the grafting procedure.

The results of peroperative transfusions have been controversial. In one study (11) no significant increase in graft survival was shown: 61 patients transfused during surgery did as poorly (40% six-month graft survival) as 188 nontransfused recipients. Opelz and Terasaki (14) found no significant difference in cadaveric kidney graft survival among 684 nontransfused recipients and 371 peroperatively transfused recipients. However, Corry et al (13) noted a graft survival rate in 78 patients transfused with one to three units of blood peroperatively intermediate between the rates of the never-transfused and the previously transfused patients. Spees et al (15) in their study of 1,907 cadaveric renal transplants found no beneficial transfusion effect with frozen RBCs, packed RBCs, or mixed RBCs given peroperatively. However, these authors noted improved survival when packed RBCs and mixed RBCs were given within ten days to one year pretransplant.

Posttransfusion Sensitization. The widespread fear of sensitization has been tempered somewhat by success with pretransplant transfusions, but concern nevertheless continues. Soulillou et al (16) showed that after four blood transfusions, cumulative immunization averaged 90%. They also noted that anti-B lymphocyte (63%) was more frequent than anti-T lymphocyte (49%) immunization. Despite the high rate of immunization, however, the majority of patients developed narrow-spectrum antibodies, that is, less than 30% of the panel killed. Terasaki (17) noted that only reactivity greater than 90% was associated with significant decrease in graft survival. Therefore, it is important to study the kinetics of lymphocytotoxic antibodies. According to Terasaki's data (17), the risk of developing panel reactivity greater than 90% is small. In 550 patients, 4% reached that broad level of reactivity after five transfusions, 7% after ten, and 12% after twenty transfusions.

Soulillou's group found different patterns of lymphocytotoxins after blood transfusions (16). Anti-B lymphocyte antibodies were greatest on day eight after transfusion and then decreased in frequency, while anti-T lymphocyte antibodies developed later, at day twenty-one after transfusion.

What has caused confusion in the literature has been the cut-off point for broad reactivity. Terasaki has used a 90% level, whereas other authors (18) have defined broad reactivity as 10% anti-T and 20% anti-B lymphocytotoxins. One year later the same authors raised the exclusion thresholds to 15% for anti-T and to 40% for anti-B lymphocytotoxins because they believed the latter antibody was not deleterious to graft survival.

Iwaki et al (19) further delineated the antibody question. In a small prospective study of 25 patients, they found a beneficial effect with development of cold-reactive (5°C) anti-B lymphocyte antibodies, while warm-reactive (37°C) antibodies to B lymphocytes had a deleterious effect on the grafted kidney. Antibodies to donor T cells are associated with hyperacute or accelerated graft rejection. Presumably, cold-reactive antibodies react to immunoglobulins on B lymphocytes, while those that react in the warm temperature are usually HLA-DR antibodies (20). An interesting phenomenon has been observed by some investigators: patients who developed antibodies and subsequently lost them had much better graft survival than patients who never developed lymphocytotoxins (21).

HLA Matching. There are two opposing schools of thought regarding the effect of blood transfusions and the HLA match of renal grafts. Some believe the HLA match is of paramount importance, while others believe the blood transfusions exert their effect regardless of the HLA match. Fehrman (7) noted improved graft survival in patients receiving pretransplant blood transfusions when the kidney graft HLA incompatibilities were two or less, but not when there were three or four incompatibilities. Van Es (22) noted poorer graft survival as the number of HLA A and B mismatches increased. Graft survival at six months was 86% when there were no mismatches, but fell to 68% with one mismatch and fell further to 54% with two mismatches.

Opelz and Terasaki (8) support the dominant effect of blood transfusions on graft survival. Greater graft survival was observed in patients with a four-antigen mismatch and more than ten transfusions than in patients with zero mismatches and no transfusion. Thus, in patients with no transfusions, HLA match was important in graft survival. With few transfusions, correlation of HLA match with graft survival was weak; when there were more than ten transfusions, HLA match had no correlation with graft survival.

Spees et al (9) have taken an intermediate viewpoint. They believe that blood transfusions are the dominant factor in cadaveric renal transplant survival, and that HLA matching provides additional benefit. It accounted for a 9% improvement in graft survival in those of their patients who not only received blood, but also had a high HLA match.

There has been a suggestion that matching for HLA-DR determinants is an important factor in cadaveric renal transplant survival. A prospective study by Persijn et al (23) concluded that HLA-DR matching and blood transfusions have a synergistic beneficial effect on graft survival.

Mechanism of Blood Transfusion Effect. There have been many speculations on the mechanism by which blood transfusions enhance renal graft survival, but the answer remains unclear. Proposals have included modification of the host immune system and selection (by antibody formation) of patients in whom graft survival will be prolonged (24).

The population of patients requiring renal transplantation may also be unique with regard to changes in the immune system. It was observed that patients with chronic renal failure and regular dialysis treatment had reduced cell-mediated immunity (25). These patients also suffer from nutritional imbalances, which may have nonspecific effects on the immune system. It has been suggested that endocytosis and lysis of transfused RBCs may result in suppression of the cellular response to antigenic stimulation (26).

If the host immune system were to develop suppressor cells (induced by blood transfusions), these cells could function by inhibiting donor-specific cell-mediated lymphocyte destruction (27). Cochrum et al (28) studied donor-specific transfusions and renal graft survival. They found no significant change in mixed lymphocyte culture reactions before and after transplant. However, there was a decrease in cell-mediated lympholysis after transplantation, even in patients with high pretransplant values. However, these patients did not lose their high values of cell-mediated lympholysis when challenged with third-party cells.

Smith et al (29) studied fifteen renal dialysis patients in the hope of supporting the suppressor-cell induction hypothesis. They observed that, after a single transfusion of two units packed RBCs, suppressor cell function decreased at one week after transfusion, then increased at three weeks, but subsequently declined over the ensuing three to five months. They, therefore, encouraged timing the renal transplantation procedure between three weeks and three months after transfusion.

Studying 48 uremic patients, Fehrman and his co-workers (30) noted a decrease in mixed lymphocyte culture reactivity when compared with normal control patients. Of interest was the even lower reactivity noted in uremic patients who had received more than twenty blood transfusions.

When recipient blood was B-cell depleted, and the experiments reperformed, these authors observed an increase in mixed lymphocyte culture reactivity. Since it was not known that mixed lymphocyte culture reactivity was inhibited by sera containing anti-HLA antibodies, these findings led them to hypothesize that the recipient B cells produced polyclonal antibodies which may have masked donor cell antigens and thus resulted in low mixed lymphocyte culture reactivity.

There is increasing acceptance of a selection effect with regard to pretransplant blood transfusions and renal graft survival (10). The risk of developing broad-spectrum HLA antibodies increases with an increased number of blood transfusions. Once a patient develops these antibodies, it is difficult to find a matched kidney for transplantation. However, if such a kidney is available, it is very highly matched for HLA A and B. It is believed by many investigators that a match for HLA A and B is associated with improved graft survival. Therefore, the apparent success of pretransplant transfusions may be due entirely to the process of selection. A patient who has had many transfusions and cannot be transplanted does not enter the analysis and a patient who can be transplanted has the benefit of an excellent HLA match and is, therefore, selected for improved graft survival.

Prospects. Transfusion trials are in progress at many transplantation centers. Based on published reports and individual experience, future modifications of transfusion protocols promise advancements in the field and the hope of even more prolonged graft survival.

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Submitted for publication September 1982.

Nominations Open

Lita Annenberg Hazen Awards
for Excellence in Clinical Research, 1984

Nominations of outstanding physicians or physician investigative teams working at any institution in the world are invited for the 1984 Lita Annenberg Hazen Awards for Excellence in Clinical Research. These awards, made to encourage increased participation in clinical research by physicians, are administered by the Mount Sinai School of Medicine (CUNY). The award committee is composed of fifteen eminent specialists in a variety of disciplines working at eleven institutions throughout the United States.

Two prizes of $50,000 each are awarded, one (tax-free) to a physician-investigator or an investigative team whose achievement and potential for future breakthroughs in clinical research are outstanding, and the second to a research fellow or fellows selected as associates by the award winner.

To obtain the nomination form and a complete description of the nominating procedure, or for further information of any kind, contact Thomas C. Chalmers, MD, Chairman, The Lita Annenberg Hazen Awards, Mount Sinai School of Medicine, l Gustave L. Levy Place, Annenberg 24-64, New York, NY 10029, or call (212) 650-8832.

The Mount Sinai Journal of Medicine
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Stress and Diseases of the Upper Gut: III. Gallbladder Disease

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Abstract

The pathological changes reported in acute acalculous cholecystitis are mucosal ulceration, necrosis, gangrene, and perforation. The inference is that one of the primary effects of the stressors (surgery, trauma, burns, drugs, sepsis, shock, and certain medical illnesses) is hemodynamic.

Stress and gallbladder disease as a subject has never appeared as a title in the literature. However, the scenario for the role of stress in the development of acute acalculous cholecystitis could be predicted on the basis of studies of stress ulcers (1), stress and liver disease (2), and stress and pancreatic disease (3). Indeed, the same stressors, namely, postoperative effects, trauma, burns, drugs, sepsis, shock, and certain medical illnesses, figure in the etiology of these various diseases.

No one specific surgical procedure predisposes to acute acalculous cholecystitis. Among the abdominal operations that have precipitated cholecystitis are appendectomy, gastrectomy, small bowel resection, and hemicolectomy (4–7). However, this complication has also followed nonabdominal surgery, including various orthopedic procedures, transurethral prostatic resection, lobectomy, cardiac valve replacement, and scalene biopsy (4–8).

Trauma, both local to the abdomen (4, 9, 10) and not direct to the viscera, can be a precipitating factor. Nonabdominal injuries predisposing to cholecystitis include fractures of various bones of the pelvis (8) and of the extremities (4, 9).

Burns, electrical (10) and thermal (8, 11–13), and drugs, particularly thiazides (14) and oral contraceptives (15), may antecede an attack of acute acalculous cholecystitis. Pneumonia (4, 8, 16) and acute urinary tract infections (4) are septic conditions known to have precipitated attacks. Myocardial infarction (4), stroke (4), and polyarteritis nodosa (17) are among the medical illnesses found to be etiological factors.

Pathologic Findings and Pathogenesis. The pathological findings of acute acalculous cholecystitis are significant in determining the pathogenesis. Rice's descriptions of the gallbladder in his six reported cases (11) were as follows:

1. distended and partially necrotic
2. acutely inflamed with mucosal micro-abscesses and mucosal ulcerations
3. necrotic
4. markedly inflamed with small areas of necrosis
5. gangrenous
6. inflamed with focal necrosis.

Wolfson and Rothenberg submitted thirty-one cases with the observation that the cholecystitis was acute suppurative in 16, gangrenous in 12, acute hemorrhagic in 1, phlegmenous in 1, and acute ulcerative in 1 (16). Among the pathological findings in Robertson's report were mucosal ulcerations in 38%, multifocal necrosis in 41%, mass gangrene in 14%, and perforations in 23% (4). The frequency of the findings of ulceration, necrosis, hemorrhage, and perforation confirm hemodynamic involvement.

This is in agreement with Glenn et al; after some thirty-five years of study of acute acalculous cholecystitis, these authors concluded: "Histologically, the common feature in these cases consisted of intense injury of blood vessels in the muscularis and serosa of the gall bladder" (8).

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Limited Blood Supply. According to the textbook descriptions, the gallbladder usually derives its total blood supply from a single vessel, the cystic artery. This is a branch of the right hepatic artery, near its origin from the common hepatic artery. Since it has been demonstrated that various stress factors are responsible for reduction in blood flow to the stomach, duodenum, pancreas, and liver, it is realistic to assume that stress factors produce ischemic changes in the gallbladder. This resulting vasospasm is responsible for the hypoxia or anoxia. Inasmuch as this viscera has such a limited blood supply, the severity of the hypovolemia and hypoperfusion results in varying degrees of change: ulceration, necrosis, gangrene, perforation.

Acknowledgments

The authors are very grateful to the librarian of the Touro Infirmary, Patricia J. Greenfield, and her assistant, Mary E. Hess.

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Submitted for publication November 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Managing Dyspepsia in Gallstone Patients

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Dyspeptic symptoms such as the feeling of being filled after a meal, epigastric discomfort, acid eructation, nausea, epigastric burning, and so forth have been observed among 80% of gallstone patients (1). Cholecystectomy has been found to relieve the dyspeptic symptoms of 70%–75% of all patients (2); the remaining 25%–30% continue having the same dyspeptic symptoms postoperatively.

Because it has been claimed that dyspeptic symptoms are related to duodenogastric reflux (3), and because the percentage of patients that continue to have dyspeptic symptoms after cholecystectomy is high, we conducted a study of the correlation of dyspeptic symptoms with duodenogastric reflux among gallstone patients which also examined the role of cholecystectomy in managing dyspeptic symptoms.

Subjects and Methods

Our research subjects were 47 patients, 36 women and 11 men, aged 23 to 69, treated for cholelithiasis at the A Propaedeutic Surgical Clinic during the 16 months from October 1981 through May 1982. Of the 47 patients, 33 (70.4%) reported dyspeptic symptoms; the other 14 (29.6%) experienced symptoms of biliary colic without dyspeptic symptoms.

All 47 patients were examined preoperatively for duodenogastric reflux, using the following method: A nasogastric tube was placed at the first-second part of the duodenum under continuous radioscopic examination and a contrast medium, 50 cc of gastrographine, was injected. Observation for reflux of the contrast medium in the stomach was maintained for 30 minutes. At the same time all the patients underwent radiological examination of the upper gastrointestinal tract to verify the probable coexistence of gastroduodenal ulcer.

After this preoperative study, and regardless of the result, we performed cholecystectomy in all patients. Three to six months after the cholecystectomy, we reexamined the patients and reconsidered the occurrence of duodenogastric reflux.

Results

Of the 33 patients who preoperatively reported dyspeptic symptoms, 10 (30.3%) had duodenogastric reflux (+D.G.R.), whereas 23 (69.7%) did not show reflux of the skiagraphic substance toward the stomach (−D.G.R.). Of the 14 patients who did not report dyspeptic symptoms at the preoperative stage, only one (7.1%) had duodenogastric reflux; the remaining 13 (92.9%) did not (see table).

In group A, the 10 patients with dyspeptic symptoms and duodenogastric reflux, cholecystectomy abolished dyspepsia in only 2 patients (20%). In group B, the 23 patients with dyspeptic symptoms but without duodenogastric reflux, cholecystectomy relieved 19 patients (82.6%). The other 4 patients (17.4%) experienced dyspeptic symptoms as long as 6 months after cholecystectomy (see table).

The patients in groups C and D did not have any postoperative problem.

In the 11 patients with verified preoperative duodenogastric reflux, cholecystectomy did not alter the phenomenon of reflux, whether the patient did or did not have dyspeptic symptoms.

Discussion

From time to time a variety of views on the frequency and interpretation of dyspeptic symptoms of gallstone patients have been supported.

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Relation of Dyspeptic Symptoms to Duodenogastric Reflux and Cholecystectomy (47 Patients)

	Dyspeptic Patients				Nondyspeptic Patients		
	n	%	group	Post-Operative Relief n (%)	n	%	group
+DGR	10	30.3%	A	2 (20%)	1	7.1%	C
−DGR	23	69.7%	B	19 (82.6)	13	92.9%	D

In 1963 W. H. Price maintained that the frequency and the seriousness of dyspeptic symptoms have no relation to the presence or absence of gallstone and that the dyspeptic symptoms are distributed among gallstone patients casually (4). A different view was expressed in 1968 by Rhind and Watson (5), and by Gunn and Keddi (1) in 1972, as well as in more recent works by Kingston and Windsor (2) and Johnson (3), who claim that there is a direct relation between dyspeptic symptoms and cholelithiasis; they argue that cholecystectomy rids 75% of the patients of their dyspeptic symptoms. Capper et al (6) reported duodenogastric reflux which resulted in the atrophy of the gastric mucous glands, which causes dyspeptic symptoms.

Johnson (3) conducted a radiologic and sample check of the duodenogastric reflux with simultaneous measurement of pressures at duodenum and stomach. The author claimed that the patients who had dyspeptic symptoms had a higher frequency of duodenogastric reflux than those without dyspepsia and that the relief of dyspeptic symptoms after cholecystectomy was correlated with decrease of the duodenogastric reflux.

Sleisenger and Fordtran (7) report that under normal circumstances cholecystokinin released after a meal causes contraction of the duodenum and the gallbladder, while simultaneously the emptying of the stomach is slowed down (closed pyloric sphincter). Among certain gallstone patients, the duodenum which is filled with bile contracts when the pyloric sphincter is open; this results in reflux of the bile from the duodenum to the stomach and produces dyspeptic symptoms.

In our study of 47 gallstone patients, the percentage of duodenogastric reflux among patients with dyspeptic symptoms amounts to 30.3% of the cases, whereas among the patients without dyspeptic symptoms the percentage was only 7.1%. Thus in this clinical research, it seems that duodenal gastric reflux is more frequent among gallstone patients with dyspeptic symptoms than among those without dyspepsia. Our second finding was that cholecystectomy in patients with dyspeptic symptoms and duodenal gastric reflux relieved only 20% of the patients from their dyspeptic symptoms. However, cholecystectomy in patients with dyspeptic symptoms but without duodenal gastric reflux resulted in the obliteration of indigestion of 82.6% of the patients.

The results of this study are similar to those of Rhind and Watson (5), Kingston and Windsor (2), and Johnson (3). However, these authors claim that relief of dyspeptic symptoms after cholecystectomy was on occasion accompanied by diminution or disappearance of duodenal gastric reflux; we did not observe anything similar in any of the 47 patients.

Summary

We studied 47 gallstone patients for the existence of dyspeptic symptoms and duodenogastric reflux, and assessed the results of cholecystectomy on these parameters. Among our patients there was a close relation between flatulent dyspepsia and duodenogastric reflux. For those patients with dyspepsia and duodenogastric reflux, cholecystectomy relieved dyspeptic symptoms in up to 20%. For patients with dyspepsia but without duodenogastric reflux, cholecystectomy relieved dyspeptic symptoms in up to 82.6%.

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Submitted for publication February 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Management of Permanent Colostomy

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Because of the many problems involved in the care and rehabilitation of patients with permanent iliac colostomy, enterostomal therapy is being used with increasing frequency in many countries throughout the world. A good functioning iliac stoma is essential to the success of the Miles operation if the patient who has a satisfactory stoma (Figs. 1, 3) is to return to a normal social and working life.

There has been close cooperation between surgeon and psychiatrist in the preoperative stage for the last two years in the Emergency Surgery department and Ostomy Care Center at the University of Bari in Italy. The purpose of the project reported here was to see what approach to the patient is needed to prevent, or at least to limit, serious psychological problems. The management of patients in whom a colostomy is to be created goes through four fundamental chronological stages; our work plan is outlined in Table I. The therapeutic course was divided into two areas, medical treatment and psychological care. Following a decision to operate, the patient's personal history was carefully evaluated prior to telling him or her of the decision. This communication was done with particular care. Psychological intervention, including short-term psychotherapy, was required during this preoperative stage. The purpose was to estimate the patient's degree of emotional response to the diagnosis and to determine if the patient could tolerate the procedure psychologically. Frequently the first reaction was refusal; following this, however, the patient would think it over, and most accepted it. The family was necessarily involved in the acceptance process, and the function of the colostomy—a normal variation of normal daily functions—was carefully explained to family members. After the operation, psychotherapy was continued in order to begin the slow psychological separation of surgeon and patient. Following discharge, some of the patients who were seen at the Ostomy Care Center for periodic checkups required and received further psychotherapy. When necessary, the surgeon requested psychiatric help, or prescribed drugs, or did both.

Operative Care and Postoperative Complications

Great care was taken in siting the stoma; the site was precisely marked in the preoperative period. The complications occurring immediately after surgery are enumerated in Table II. Excellent stoma control was insured by applying adherent open-end bags immediately after the operation, resulting in adequate protection of prestomal skin. In the postoperative period the

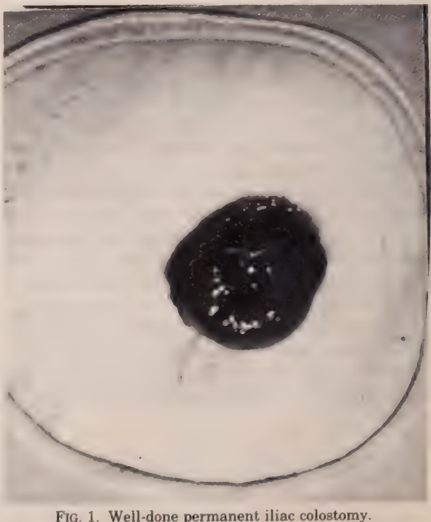

FIG. 1. Well-done permanent iliac colostomy.

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Paper presented at the fourth I.O.A. Congress, July 13–16, 1982, Munich.

relationship between the enterostomal therapist and the patient was developed, the goal being complete rehabilitation.

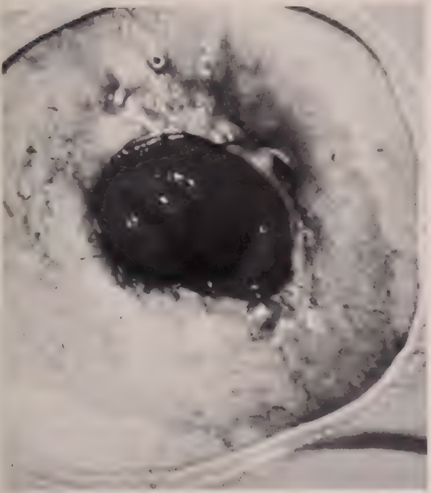

FIG. 2. Granuloma caused by omitting to remove stitches.

Long-Term Follow-up

Detailed examination of the main problems was carried out at various intervals following surgery over a five-year period. Long-term physical problems are enumerated in Table III; psychological problems are listed in Table IV. Stoma-related complications recorded at the Ostomy Care Center at the University of Bari in Italy are shown in Table V. The first year after the operation is an experimental period aimed at achieving control of spontaneous intestinal motility.

TABLE I
The Four Stages in Colostomy Management

Preoperative Stage
Request for cooperation of patient or relatives
Decision on site of stoma
Same therapeutic and follow-up program for all patients
Operative Stage
Choice of most suitable operative technique
Opening of stoma, immediate or after 24–36 hrs
Application of adhesive, transparent open-end bags
Postoperative Stage
Protection of skin (proper bags or appliances)
Check of stomal lumen
Initiation of relations with enterostomal therapist; beginning of rehabilitation treatment
Removal of peristomal suture stitches
Stabilization Stage
Regulation of alvus: diet, prevention and care of local complications; continence; use of drugs
Management of stoma; suitable appliances
Return to social life
Clinical follow-up

Psychosocial Problems. Symptoms of postoperative depression included reaction to the loss of the anal sphincter; worry about not being able to avoid soiling oneself; sense of mutilation; feeling of greater fragility and less attractiveness of the body; sense of lacking dignity; unexpressed anger against the surgeon as responsible for the mutilation; no faith in the possibility of rehabilitation. Fifty percent of the patients also had various

TABLE II
Immediate Physical Complications of Permanent Colostomy

Pathology	Cause	Treatment
Necrosis	Ischemia	Operation
Separation	Poor technique	Operation
Eventration	Parietal dehiscence	Operation
Obstruction	Poor technique	Operation
Stomal defects	Poor technique	Possible operation
Prolapse	Suction appliance No mucocutaneous suture	Proper instruction
Peristomal fistulas	Stitches piercing colon	Possible operation
Hemorrhage	Small open arterioles Fragile superficial mucous vessels	Proper instruction
Peristomal granuloma	Stitches not removed	Proper instruction
Infections (cellulitis)	Sepsis Partial separation of stoma	Possible operation

Adapted from Goligher (2).

TABLE III

Later Physical Complications of Permanent Colostomy

Pathology	Cause	Effect	Treatment
Intrusion	Obesity Healing retraction	Stenosis	Possible operation
Skin stenosis	Sepsis and stomal dehiscence; long outer colon stump General diseases (Addison's disease)	Obstruction	Possible operation
Prolapse	Insufficient stitching Suction appliance No mucocutaneous suture	Possible dermatitis	Possible operation
Peristomal hernia	Too wide opening in the abdominal parietes Parietal dehiscence		Proper instructions or operation
Stomitis	Enteritis		Proper instructions
Peristomitis	Bad local hygiene	Appliance difficult to fit	Proper instructions
Mucosal bleeding	Vascular disturbance of loop		Proper instructions

Adapted from Goligher (2).

other "neurasthenic" symptoms (headaches, weakness, sweating, dizziness, insomnia, irritability, gastralgias, "peristomal pains," and nightmares about death).

From a psychosexual point of view, despite difficulty in getting precise data and the lack of a control group, the survey produced the following results: excellent adaptation within marriage, 100%; enjoyment of sexual intercourse, 80%; interest in sex decreased, 15%; increased, 10%. The frequency of sexual intercourse returned to the preoperative level after a period of relapse. In elderly people there was a drop in sexual activity, but the drop in male potency was not more than 15%. In patients identified as psychopathological (10%), the negative side of the personality was emphasized. In 15% of the cases there was a significant reduction in work capacity. There was, moreover, a drastic reduction in the pursuit of hobbies and in general enjoyment of life. All these are aspects of the problem of deterioration in social relations, which can reach the point of a complete break in contact with other people (20% of the cases).

TABLE IV

Incidence of Main Psychosocial Problems in Permanent Colostomy

	% cases
— postoperative depression	55
— neurastheniform symptoms	50
— change in body image	40
— phobias	34
— obsessiveness	30
— diet problems	22
— deterioration in social relations	20
— financial problems (cost of adhesives, soap, bags)	15
— reduction of work capacity, interruption of work	15
— psychosexual difficulties	15
— emphasis of psychopathological traits	10
— no problems	8

The two defense mechanisms most used by pa-

TABLE V

Follow-up of Stoma-Connected Symptoms

	No.	Development	Treatment (No.)
Peristomal Skin			
Normal	30		
Erythematous	26	Improvement	Instruction
Ulcered	1	Improvement	Instruction
Eczematous	1	Improvement	Instruction
Keloidial	7	No change	Instruction
Stoma			
Congestion	13	Improvement	Instruction
Bleeding	10	Improvement	Instruction
Retraction	7	No change	Instruction
Prolapse	9	Improvement	Operation (2)
Stenosis	5	No change	Operation (1)
Eventration	14	Worsening	Instruction (12) Operation (2)
Alvus			
Stipsis	10	Improvement	Instruction
Liquid feces	5	Improvement	Instruction
Semiliquid feces	17	No change	Instruction
Semisolid feces	29	No change	Instruction
Solid	26	No change	Instruction
Continence			
Possible "wash-outs"	15	Excellent	Diet and bags; no cases treated with Maclet or magnetic ring

tients to protect themselves from postoperative anxiety were phobias (34%) and obsessive behavior (30%). The less successful mechanism is that of phobia (premature aging). Obsessive behavior achieves better results. These characteristics (7.5% of the cases) improved with time, rehabilitation, and suitable psychotherapeutic and psychopharmacological measures; return to normal social life was good in 70% and excellent in 16% of the cases. Better results were obtained when the patients were assisted from the preoperative stage.

Physical Complications. At present a number of "aids" for colostomy can avoid the more common local discomforts connected with a stoma: uncontrolled loss of feces and flatus, irritation of the stoma and the surrounding skin with eruption of allergies, eczema, dermatitis, erythema, itching, keloid (Figs. 3-5). From the data collected in the survey the following can be seen:

Peristomal skin was normal in 30 ostomate patients; erythematous in 26 and ulcered in one case. Peristomal pathology improved with use of suitable therapy and proper instructions.

Stoma. Initial congestion seen in 13 cases improved later on; initial bleeding in 10 cases also improved. Stoma prolapse (nine cases) did not get worse; retraction (seven cases) did not change. One stoma was redone.

Eventration, seen in 14 patients, increased in the later check-ups. Proper surgery of the stoma is therefore necessary to avoid this common complication (Figs. 6, 7).

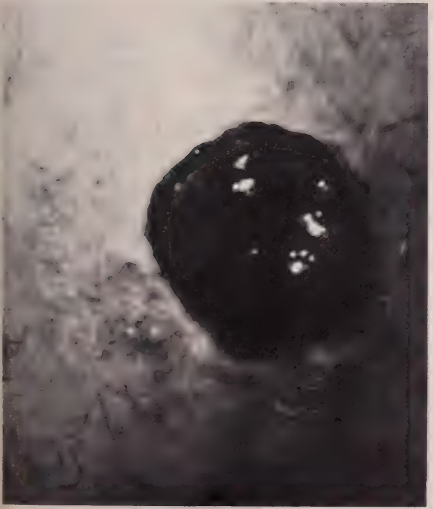

FIG. 3. Slight peristomal dermatitis.

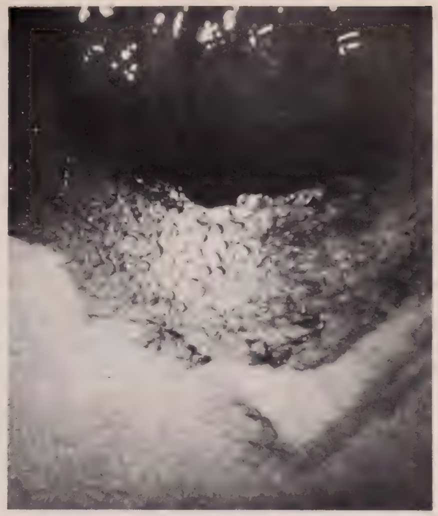

FIG. 4. Peristomal dermatitis; slight prolapse.

Alvus. Regulation of the alvus by good information on the diet ensured improvement of stipsis (initially seen in 10 patients).

Continence. It was not possible to begin or follow up instructions of "wash-out" in all patients for reasons of age or general condition (regularly adopted in only 15 cases). Continence of feces was observed in 15 cases undergoing wash-out and feces and flatus in 12. The stomal bags were ad-

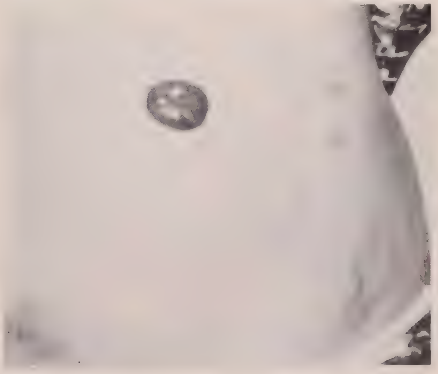

FIG. 5. Dermatitis caused by allergy.

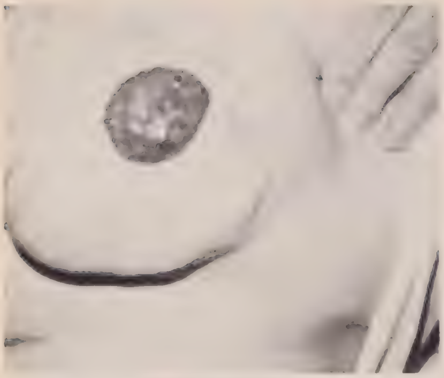

FIG. 6. Eventration.

equate in 52 patients, but clearly inadequate in 13, who sustained eruption of eczema from hypersensitivity to the adhesive and difficulty in applying the bag properly because of the awkward position of the stoma.

The problem of continence should soon be solved by wide use of the magnetic closure system, Erlangen type (Maclet). The results achieved by surgeons Feustel and Henning in 1975 and Goligher in 1977, the first to use them, encourage the rosiest expectations. However, the problem of necessary stomal assistance is still unsolved (see Table V).

Endoscopic follow-up. Ostomate patients operated on for neoplasias must undergo routine transstomal endoscopic check-ups. In 39 patients who underwent endoscopic follow-up more than six months after surgery, two polypoid lesions (adenomas), one multiple polypoid lesion (adenoma) and one neoplastic recurrence were identified. In these four patients the lesion was asymptomatic. However, coloscopic control, at least once a year, can furnish indications on the development of the disease and the treatment to be undertaken.

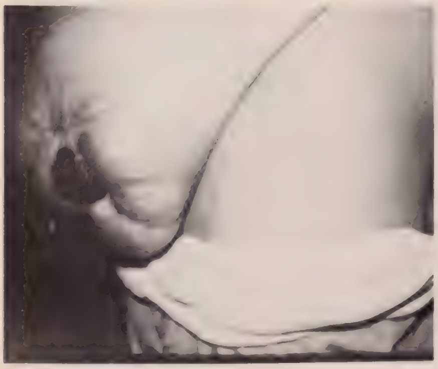

FIG. 7. Large eventration.

Conclusions

Although long-term physical complications of the stoma are not very common, psychosocial complications are. Thus the solution of problems of psychological organization and social reintegration of ostomate patients is of fundamental importance. In rehabilitation centers, with the aid of specialists (surgeon, psychiatrist, dietician, enterostomal therapist) and volunteer workers, reliable guarantees can be given to patients. To maintain and increase this support, schools and courses of specialization for suitable personnel, additional welfare facilities, social meetings for ostomate patients, support by health authorities, and better public understanding are all necessary.

Summary

The successful postoperative management of a permanent iliac colostomy performed after a Miles operation depends on (a) proper surgical technique for ostomy, and (b) the cooperation of the patient. There have been only a limited number of patients who were treated for rectal cancer. Of 12 patients operated on, no serious local complications have been observed, and only four patients developed slight complications, such as light stomal bleeding and peristomal skin infections. Use of modern colostomy "aids" allows a direct view of the stoma, blocks infiltration of matter and air, and slows down the action of the intestinal microflora, thus avoiding the adverse effects (prolapse or stomal erosions) caused by earlier methods. Another advantage in using these aids is that they prevent weakening of the peristomal skin. Thus the immediate opening of the colostomy is possible and the routine rehabilitation treatment, in collaboration with enterostomal therapists, may begin.

A five-year study, carried out by the A. I. Stoma Care Centre in Bari, Italy, on 65 ostomate patients with rectal cancer, allowed us to describe the exact evolution of the pathologic features related to colostomy. Thirty per cent of the cases were followed up at weekly intervals, and 50% were followed up monthly. The ostomy pathology of the peristomal skin and irregular bowel behavior may be improved by adopting adequate

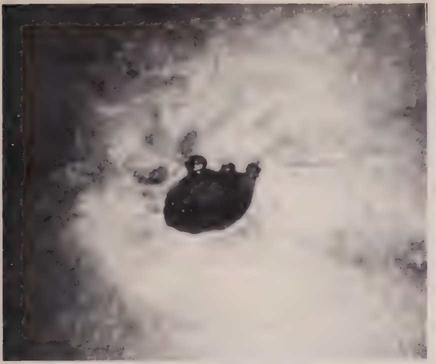

FIG. 8. Stenosis.

therapeutic measures. However, this was not the case for stenosis (Fig. 8) and herniation; three patients with these complications required surgical treatment. Regular washouts were possible in only 15 patients. Even though no symptoms were noted, the ostomy-endoscopic follow-up showed one neoplastic recurrence and three polypoid lesions.

Of the psychological problems related to permanent iliac colostomy, the most common, especially in women, were depression, phobias, obsessiveness, hypochondria, reduction of working capacity, and the deterioration of social relations. These patients were treated with adequate therapeutic measures and responded to the treatment: 53 patients readapted reasonably well and 12 extremely well. Patients who underwent preoperative care improved rapidly; we conclude that better results are obtained if patients are followed from the preoperative stage on.

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Submitted for publication November 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Liver Scan in Hepatic Amebiasis: Correlation With Clinical and Biochemical Studies

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Abstract

A series of 1,225 consecutive liver scans was analyzed to determine incidence of hepatic amebiasis and usefulness of scans compared to clinical findings and standard biochemical liver function tests. The results in this series are compared to those in published series. Of 1,225 scans, 202 (16.5%) were proved hepatic amebiasis (107 "abscess," 95 "hepatitis"). Amebic abscess was the most common single focal liver defect (41.5%), suggesting that where amebiasis is prevalent, two out of five hepatic focal defects could be due to amebic abscess. Liver and spleen weights were high in amebiasis cases, even higher in abscess cases. The majority of abscesses were single, in the right lobe, most commonly on the anterior surface. Hepatic amebiasis was seen mostly in young adult males, associated with significant anemia, leukocytosis, hypoalbuminemia, and raised serum transaminases and alkaline phosphatase. Jaundice (27%) and splenomegaly were most commonly associated with large central or inferior surface abscesses. Splenomegaly was better diagnosed by scan than clinically. Scanning was found to be more accurate in diagnosing and localizing amebic abscess than any other single liver function test studied. Serum alkaline phosphatase, one of the most sensitive liver function tests, was found to be falsely negative in 36.7% of cases diagnosed as hepatic amebiasis. Further, scanning has the advantage of being simple, safe, and noninvasive. It is recommended in all cases of hepatic amebiasis.

Radioisotopic hepatic scan is a relatively simple, safe, innocuous, and noninvasive procedure that can be performed even on a moribund patient. It delineates size, configuration, and site, as well as defines, with remarkable accuracy, the extent of functioning liver tissue, with insignificant amount of radiation to the patient (1–19). It can be used for detecting and localizing focal defects in the liver, as well as for estimating, through recognised formulae, mass (weight) of the liver in vivo (20). Because of this, it has gained widespread acceptance in the evaluation of liver disease, particularly focal defects (21).

We record here our experience with liver scanning in 202 patients with hepatic amebiasis. The study aimed at determining the incidence by age and sex of hepatic amebiasis in a large series of liver scans, frequency of involvement of various lobes and surfaces and relation of site to various liver function tests, jaundice, and splenomegaly. Liver and spleen weights were calculated, statistically analyzed, and compared in normal controls and in patients with amebic hepatitis and amebic liver abscess. The frequency of abnormal liver function tests (transaminase and serum alkaline phosphatase) were determined and compared for accuracy with the scans. The literature was reviewed and recorded results were compared with results in this series.

Material and Methods

A consecutive series of 1,225 liver scans was performed on a high-speed rectilinear dual-head scanner with either ^{99m}Tc sulfur colloid or ^{131}I rose bengal over a four-year period (1975–78), on patients referred for clinically suspected liver disease. Of these, 657 (53.6%) were hospitalized and 568 (46.4%) were outpatients. Background clin-

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ical and laboratory information, where available, was recorded and used to arrive at a final diagnosis. In each case, anterior, posterior, and right and left lateral scans were performed, all in the supine position. Serial scans, where indicated, were performed to determine progress or response to therapy.

Diagnosis of hepatic amebiasis was based on history of intestinal amebiasis, presence of tender hepatomegaly (when other causes were clinically excluded), suggestive hematological and radiological findings, hepatomegaly and patchy uptake on scan with or without cold areas, histopathologic studies when possible, and response to antiamebic therapy. The cases thus judged to be hepatic amebiasis were classified as amebic abscess if a cold area was present on the scan and as amebic hepatitis if a cold area was absent. This distinction was not histopathologic. The inability of a scintiscanner to definitely pick up a focal lesion of less than 2 cm was established when this classification was adopted. In other words, those cases designated as amebic hepatitis could have a small focal defect of less than 2 cm which was not clearly delineated on the scan, despite four views being taken.

Results

Of the 1,225 liver scans, 258 (21%) showed space-occupying lesions. Of these, 107 (41.5%) proved to be amebic abscess. An additional 95 cases were diagnosed as amebic hepatitis. Thus, a total of 202 cases were diagnosed as hepatic amebiasis, an incidence of 16.5%.

Among the 202 patients with hepatic amebiasis were 152 males (75%) and 50 females (25%). Hepatic amebiasis seems to be a disease of young males; 78% of our cases occurred in the 21–60 age group (Fig. 1). However, this distribution does not significantly differ from the total series of scintigraphic studies.

Pain in abdomen (72%), fever (46%), diarrhea (10%), nausea or vomiting (20%), jaundice (18%), anorexia, and asthenia were the common symptoms. Onset of symptoms was either acute, subacute, or chronic. Symptomatology, in general, was more acute and pronounced in abscess than in hepatitis.

Of hematologic and biochemical abnormalities in hepatic amebiasis, anemia, leukocytosis, hypoalbuminemia, jaundice, and raised serum transaminases and serum alkaline phosphatase were seen in both amebic hepatitis and abscess, more significantly in the latter (Table I). Of 107 amebic abscesses, 88% were single and 12% multiple; see Fig. 2 for lobe and surface distribution.

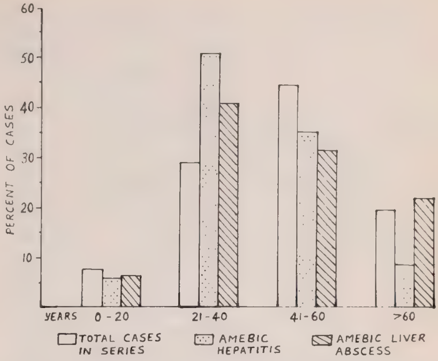

FIG. 1. Age distribution in hepatic amebiasis: no significant difference from total series with scintigraphic studies.

Using the formula of DeLand and Wagner (20), liver volume was calculated in cubic centimeters (cm^3) from the scan area. Assuming a specific gravity of 1, weight was calculated in grams. The average volume (weight) of the liver was 792 ± 21 cm^3 (gm) (mean ± SE) in the normal controls, 1050 ± 30 cm^3 (gms) in amebic hepatitis patients, and 1341 ± 46 cm^3 (gms) in amebic abscess patients. Thus, significant increase in the mass (weight) of the liver was noted in those suffering from amebic hepatitis and amebic abscess, more so in the latter, the difference being highly significant ($p < 0.001$). The average liver mass (weight) seems to increase with age up to the age of 60 and then decline, both in normals and in hepatic amebiasis (Fig. 3). At all ages liver mass is greater with hepatic amebiases.

Splenomegaly and Jaundice. Whereas only one case (1.1%) of amebic hepatitis showed clinical splenomegaly, two (2.2%) of these cases were judged to have splenomegaly on scan (Table II).

TABLE I

Hematologic and Biochemical Changes

	Hepatitis %	Abscess %	p
Hb (<12 gm%)	25.6	41.2	<0.05
WBC (>10,000/cmm)	42.9	82.6	<0.001
Serum albumin (<3 gm%)	0	62.5	<0.001
Serum bilirubin (>1 mg%)	17.6	36.0	<0.05
SGOT (>40 IU)	6.7	61.4	<0.001
SGPT (>40 IU)	28.6	62.0	<0.01
Serum alkaline phosphatase (>85 mU/ml)	41.2	72.1	<0.05

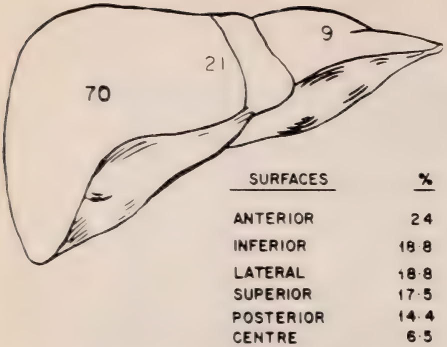

FIG. 2. Lobe and surface distribution of abscesses: predominant right lobe and anterior surface involvement.

Figures for amebic abscess were 10 (9.3%) and 18 (16.8%), suggesting that splenomegaly is better diagnosed by scan than clinically. The incidence of splenomegaly in amebic abscess was significantly higher than in amebic hepatitis. To further confirm this, splenic volume was calculated by applying the formula for an ellipse (20) (Fig. 3). Again assuming a specific gravity of 1, the average volume (weight) of the spleen in normals was 130 ± 6 cm^3 (gm), in amebic hepatitis and abscess, 131 ± 10 cm^3 (gm) and 157 ± 15 cm^3 (gm), respectively. These differences are not statistically significant.

Discussion

The incidence of intestinal and hepatic amebiasis varies from country to country and even within the same country (22–25). Incidence of intestinal amebiasis varies from less than 10% to 50% (22, 25). Hepatic involvement is estimated at about 8% (25), with a range of 7.6% to 84.4% (22). Reviewing the world literature, Kapoor (19) concluded that hepatic involvement was more common in Southeast Asia and in South Africa. Incidence also depends on the method of study, being higher in clinical studies than in autopsy studies (25).

The exact incidence of hepatic amebiasis (amebic hepatitis and abscess) among those who undergo liver scanning has not been completely calculated. In 1,225 scans, an incidence of 16.5% of hepatic amebiasis and 41% of amebic abscess among subjects with focal liver defects perhaps reflects the prevalence of hepatic amebiasis in India. In a seven-year study of 950 scans, Ganatra et al (9) diagnosed 299 cases (31.5%) as hepatic amebiases. Of these, 152 (50.8%) had a space-occupying lesion diagnosed as amebic abscess. Thus, from this and other series, liver scanning seems to have made possible earlier diagnosis of hepatic amebiasis, particularly amebic liver abscess (1–4, 6–10, 13–19, 21). However, in India and perhaps elsewhere only selected hospitalized or seriously ill patients undergo hepatic scanning; this selection could explain the higher incidence in such a group and could affect calculations of the incidence in the general population. Nevertheless from our data we conclude that in countries where amebic infestation is common, two out of five focal defects in the liver could be due to amebic abscess.

We have used the terms "amebic liver abscess" and "amebic hepatitis" only to differentiate cases that show a cold area on the scan from cases that do not, the etiological factor being the same. Hepatomegaly observed in amebic liver abscess may

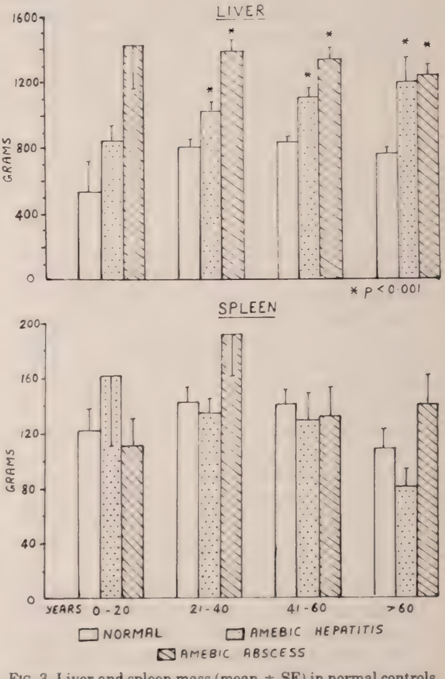

FIG. 3. Liver and spleen mass (mean ± SE) in normal controls and hepatic amebiasis: significant increase in liver mass in latter, especially with abscess, rising up to age 60 years, then declining.

TABLE II

Incidence of Splenomegaly and Jaundice and Relation to Abscess Site

	Splenomegaly %		Jaundice %
	Clinical	Scan	Clinical
Amebic hepatitis	1.1	2.2	17.6
Amebic abscess	9.3^{**}	$16.8^{\dagger ***}$	36.0^{*}
Relation to site	On Scan		On Scan
Center of lobe	40		40
Inferior surface	21		28
Anterior surface	8		27
Posterior surface	23		18
Superior surface	15		11
Lateral surface	21		10

Hepatitis vs abscess * $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$
Clinical vs scan † $p < 0.05$

be due partly to increase in size of the affected lobe and partly to reactive changes in the unaffected lobe, including edema, congestion, and infiltration (10, 11, 26). Histopathologically, the weight of evidence now available makes it unlikely that a separate entity of amebic hepatitis without abscess formation exists (27–30). Reactive changes beyond the abscess may appear on a scan as diffuse parenchymal disease (1, 4–7, 11).

Using the anatomic classification, the right lobe was involved in 70% of our cases. The incidence of right lobe involvement in other reported series (Table III) varies from 70% to 100%; left lobe involvement varies from 4% to 52% (7, 8, 12, 16–19, 22–25, 28, 31–38). The marked predominance of right lobe abscesses has been explained by the lesser bulk of the left lobe, the greater width and more linear course of the right branch of the portal vein, and differential distribution of blood in the portal vein (29).

In our series, the surface distribution of abscesses (Fig. 2) was assigned on the basis of anterior, posterior, and two lateral scans. Although the anterior surface was most commonly involved in our series, there was nearly equal distribution of lesions on the other surfaces. The surface distribution of abscesses seems to be debatable, since some researchers have described the anterosuperior surface as most commonly affected (22, 39), while others nominate the posterior surface (19, 40). This discrepancy may arise because, in some series, only one scan (usually anterior) was taken, an observation which emphasizes the importance of multiple views. Cuaron and Gordon (12), analyzing 3,379 liver scans in 2,500 patients, logically concluded that a combination of three projections (anterior, posterior, and right lateral) resulted in the highest efficiency (98.6%), depicting 99.6% of the lesions in the left lobe and 98.3% of all abscesses in the right lobe.

Amebic abscesses are usually single (Table III). The incidence of single abscesses in clinical series ranges from 73% to 100% (11, 16–19, 22–24, 32, 34, 37, 41–44), whereas in autopsy series it ranges from 47% to 65% (25, 38) (Table III). An explanation for the higher incidence of multiple abscesses in autopsy than in clinical series may be that what are apparently single abscesses often turn out at autopsy or surgery to be confluences of multiple small abscesses (38). Perhaps the incidence as determined by scan approaches that of autopsy series (Table III).

Hepatic amebiasis, particularly abscess, is universally agreed to be far more common among males (75% to 100%) (11, 14, 16–19, 22, 25, 27, 31, 32, 34–38, 45–50). Although no age group is exempt, amebic abscess is most common in young adults, 33% to 72% of cases occurring in the 21–40 age group (Table III). The exact cause of the preponderance in young men is unknown.

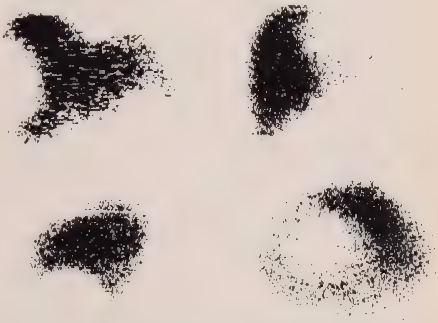

FIG. 4. Some typical scans of amebic liver abscesses: various views and sites.

The clinical symptoms observed in our series are similar to those reported by others (17–19, 22–24, 31, 36, 43, 45, 48–51). The clinical syndromes and complications arising from various regional lesions in the liver have been classically described by Kapoor (19).

Anemia and Hypoproteinemia. Anemia, leukocytosis, and hypoproteinemia are common in hepatic amebiasis, particularly with abscess (Tables I, III). The incidence of anemia varies from 15% to 100% (Table III), varying with the definition of anemia (7, 17, 18, 28, 32, 34, 37, 43, 45, 51, 53, 54) and perhaps partly related to concomitant al-

TABLE III

Reported Results, 1951–1983

Authors	Year	Total cases	Males %	Age 21–40 %	Rt. lobe %	Left lobe %	Single %	Anemia % (Hb < gm%)	Leuko-cytosis % (>10^3/cm)	Hypoalb/ abn.A/G %	Jaundice %	↑ Alk PO4ase %	↑ SGOT %	↑ SGPT %
Autopsy Series														
Purandare, Deoras (25)	1955	105(ALA)	97.0	62.0	94.0	23.0	64.8							
Aikat et al (38)	1978	79(ALA)	85.0		96.0	4.0	47.5		67.0	89.0	45.6			
Clinical Series*														
DeBakey, Ochsner (22)	1951	263(HA)	84.0	47.4	96.0	4.0	89.0				12.9			
Kean (27)	1955	50(HA)	92.0	64.0										
Lamont, Pooler (28)	1958	250(HA)				16.0		37.0(<9)						
								47.6(<12)	81.7 (>9)		10.0	28.0		
Powell (51)	1959	31(ALA)						71.0(<14.5)	74.0		0.0	17.0		
Raghavan et al (45)	1961	194(HA)	89.2	62.9				25.0(<9)	55.0		7.0			
Viranuvatti et al (46)	1963	200(ALA)	90.0	33.5						39.6	19.5	79.3		
		74(AH)	81.0	43.0						20.0	28.4	90.9	41.2	16.7
Chuttani et al (52)	1963	135(HA)							34.8(>12)		4.4			
Turrill, Burnham (31)	1966	100(HA)	85.0		97.0		98.0			61.0	11.0	78.0	57.0	40.0
May et al (32)	1967	15(ALA)	93.5		100		93.0	93(<12)	73.0	40.0	10.0			
Chhetri et al (34)	1968	50(ALA)	100	58.0	84.0	18.0	98.0	60.0	94.0	32.0	6.0	92.3	53.8	53.8
		10(AH)	100	90.0				60.0	100	10.0	0.0			
Bhaskara Reddy et al (47)	1969	35(HA)	74.0	71.0										
Aptekar, Sood (35)	1970	50(ALA)	98.0	72.0	72.0	28.0			68.0	71.0	39.0			
Subramanian et al (36)	1970	103(ALA)	99.0	56.0	98.0				24.0		7.8			
Kamat et al (42)	1970	59(ALA)					100.0			100.0	28.2	60.0	80.0	37.0
Mehta, Vakil (48)	1970	158(ALA)	92.0	48.0							22.8			
Vakil et al (49)	1970	190(ALA)	93.0	46.0							15.0			
Barbour, Juniper (37)	1972	33(ALA)	85.0	33.0	91.0		73.0	32.0(<8)	48.0(>20)	44.0	30.0	70.0	21.0	
								100.0(<13)						
Joshi et al (43)	1972	268(ALA)					77.0			35.0	23.1	18.0	14.0	17.0
Menkurkar et al (53)	1974	31(ALA)						61.3		100.0	48.4	71.0	51.6	48.4
		77(AH)						48.5		87.9	18.2	19.7	24.2	22.7
Ramchandran et al (50)	1976	137(ALA)	98.0						60.0		8.0	55.7	26.8	36.4
Adams, MacLeod (54)	1977	2074(ALA)						63.0(<12)	77.0					
Scan Series														
Tandon, Rajan (33)	1967	39(ALA)										76.9	56.4	46.9
Sheehy et al (7)	1968	17(ALA)			100.0	29.0		82.0	100.0(>15)		12.0	53.0	59.0	
Poulose et al (30)	1974	27(ALA)			92.0					63.0	11.0			
											28.5(R)			
Sharma, Jha (16)	1975	46(ALA)	100.0		81.0	19.0					40.0(L)			
Chaves et al (69)	1977	56(HA)	89.0	69.0							35.7			
Habibullah et al (17)	1977	110(ALA)	93.0	50.0	82.7	52.5		15.0(<8)	61.0		12.0	68.0		12.0
Habibullah et al (18)	1977	105(ALA)	90.0	50.0	85.0		58.0	60.0	90.0		15.0	70.0		
Kapoor (19)	1979	200(ALA)	85.0	62.5	79.0	12.0	79.0			70.0	23.1	66.0	60.0	60.0
Present series	1983	107(ALA)						13.0(<10)			36.0	72.1	61.4	62.0
		95(AH)	75.3	45.3	70.0	9.0	88.0	35.0(<12)	67.6(>10)	33.0	17.6	41.2	6.7	28.6

ALA: amebic liver abscess. AH: amebic hepatitis. HA: hepatic amebiasis.

* Includes biopsy, surgical, or autopsy confirmation.

coholism and nutritional status prior to development of amebic abscess (19). Since intestinal and hepatic amebiasis are both more common in areas where poverty is also more common, it is natural to expect anemia and hypoproteinemia in these cases (19). Although concomitant undernutrition may be common, Menkurkar et al (53), after serial liver function tests, concluded that anemia and hypoproteinemia were more common in abscesses than in hepatitis. They further concluded that anemia and hypoproteinemia were the effects of abscess and that hemoglobin and serum albumin do not return to normal after adequate treatment of amebic abscesses until up to six months of a good diet. From these studies, it appears that in a majority of cases, the more severe the damage, the greater is the anemia and hypoproteinemia and the longer the period of recovery.

Transaminase Elevations. Elevations in transaminases (SGOT, SGPT) have been reported in hepatic amebiasis in 14% to 80% of cases (Table III) (7, 17–19, 31, 33–35, 37, 43, 46, 50–53). We found elevations more commonly with abscesses than with hepatitis (Table I). The most common abnormality on liver-function test is the rise in serum alkaline phosphatase. The reported incidence varies from 18% to 91% (Table III), more commonly with abscesses (7, 17–19, 22, 28, 31, 33, 34, 37, 41–43, 46, 50–53). In a majority of reported series, more than two-thirds of cases with proved abscesses had raised alkaline phosphatase; hence this test is described as a "biochemical scanner" for space-occupying lesions in liver. Reynolds (55), however, deemphasizes the importance of this test. Although in a majority of cases, levels return to normal after healing of the abscess, nearly one-fifth of patients show raised levels as much as six months after treatment, even when repeat scans were reported normal (33). Since alkaline phosphatase can be multicentric in origin, it may be postulated that a study of its isoenzymes in the space-occupying lesions in the liver would be useful. To our knowledge no such study has been reported for amebic liver abscesses.

Jaundice and Splenomegaly. Several studies have recently reported that jaundice, once considered rare in hepatic amebiasis (23, 24, 26, 27, 32, 39, 51, 55–61), is not uncommon, particularly with abscesses (19, 23, 24, 28, 34, 36, 41–43, 49, 62). Reported incidence varies from 0 to 48.4% (Table III). The mechanism of jaundice is not clear. It is attributed to distortion and compression of the intrahepatic biliary tree by abscesses, causing cholestasis (41–43, 46, 59, 63–67). Raised serum alkaline phosphate may suggest cholestasis. Because of concomitant hypoproteinemia and elevated transaminases, it has been postulated that the mechanism was parenchymal hepatic damage (35, 43, 49, 62). In a systematic review of alterations in bilirubin metabolism in patients with amebic liver abscess, Datta (65–67) concluded that there is no increased load of bilirubin, that uptake and conjugation are apparently intact, and that the primary defect seemed to be in excretion. He showed that bilirubin UDP-glucuronic transferase levels are normal, but bilirubin excretion is impaired, with a fall in levels of BSP-glutathione conjugating enzyme accounting for the often-noted prolonged BSP retention. According to Datta, mild hepatic dysfunction may follow cholestasis, and the jaundice may be primarily cholestatic.

Though abscesses on the inferior surface would be more likely to cause biliary compression and jaundice, other researchers could not find inferior surface predominance in abscess distribution, biliary duct distortion, or any correlation between the site and size and jaundice (42, 43, 49, 60). From our data (Table II), and as suggested by Reynolds (55), however, it seems that abscesses in the center of the right lobe or the inferior or anterior surface are more likely to produce jaundice. This is perhaps in agreement with the mechanism suggested by Datta (65–67). Jaundice has also been reported to be more common with left lobe than with right lobe abscesses and with multiple rather than with single abscesses (16–19, 25, 38, 43, 44, 49, 58, 60, 63). It has been considered a bad prognostic sign in amebic liver abscesses (28), since higher mortality is reported in these cases (28, 43, 48, 49, 62).

Although clinical splenomegaly was once considered absent in amebic liver disease (39), the reports of it are sufficient to warrant a contrary view (1, 36, 38, 48, 68, 69). Clinical splenomegaly, moreover, occurs only when the spleen is more than twice normal size. One autopsy study showed a 63% incidence of splenomegaly, whereas only 2% were detected clinically (38). Rao (68) conclusively demonstrated a rise in portal pressure in amebic liver abscess, reversing after treatment. It is speculative whether the thrombosis of portal radicles (70), portal and sinusoidal infiltration (26), diffuse fibrosis (71), and wide dilatation of portal vein with increased patency of anastomotic channels (28), observed in amebic liver abscess, contribute unrecognized evidence of the etiology and presence of portal hypertension; hepatic vein thrombosis may be a major factor (38). As in jaundice, distortive processes are more likely with large central abscesses. Unlike jaundice, however, splenomegaly has not been reported to be linked with mortality.

Scan and Other Liver Function Tests. Nagler et al (3) document the usefulness of radioisotope scanning of the liver in 548 scans in which the diagnosis was confirmed by autopsy, laparotomy, or biopsy. Eighty-three percent were correctly diagnosed as positive, 88% as negative. Nagler et al concluded that a scan is superior to surgical exploration in excluding metastatic liver involvement and has the added advantage that it can be repeated without ill effects. They further concluded that a scan reported as positive for a space-occupying lesion is an important diagnostic asset when coupled with clinical data. By making possible earlier diagnosis of amebic liver abscess, scanning has substantially reduced morbidity and mortality; it also provides the surgeon with valuable localization information for determining a drainage approach (1–4, 6–19, 21). The accuracy of liver scanning is steadily improving, either due to better instrumentation or the experience of its users (21). It is more accurate in diagnosing liver space-occupying lesions than any other single liver function test (LFT), having a reported incidence of false negative in only 7%–27% and of false positive in 2%–12% (21).

In order to assess the sensitivity and reliability of hepatic scanning compared to other commonly employed LFTs, and to determine whether the information provided is merely a duplication or is supplementary, we compared our data (Table IV) on amebic hepatitis and abscess and found that whereas hepatomegaly (as judged by mass), with or without a space-occupying lesion, was present in all cases, serum alkaline phosphatase was normal in 22 (36.7%) of cases. Normal phosphatase occurred equally commonly, whatever the liver mass. Gollin et al (4) analyzed the results of 380 liver scans on 357 patients and compared them with other LFTs. Abnormal scans, indicating localized disease, were highly reliable (less than 2.5% false positive). Normal scans did not exclude focal disease, particularly occurrences less than 2 cm in size. They concluded that scans, though of limited value in detecting diffuse disease, were more sensitive than any other available method in detecting focal disease. Alkaline phosphatase was as sensitive, but yielded twice as many false positive results. Ferrante and Maxfield (72) showed scans to be more accurate than the usual LFTs and even liver biopsy. Wagner and North (73) also concluded that the scan was superior to alkaline phosphatase in sensitivity, specificity, diagnostic accuracy, and predictive value.

TABLE IV

Correlation between Scan and Serum Alkaline Phosphatase in Hepatic Amebiasis

	Serum Alkaline Phosphatase	
Liver Weight (gm)	Raised %	Normal %
Hepatitis		
Minimal enlargement (<900)	50	50
Moderate enlargement (900–1100)	40	60
Marked enlargement (>1100)	38	62
Mean (i)	41	59
Abscess		
Minimal enlargement (<900)	0	100
Moderate enlargement (900–1100)	78	22
Marked enlargement (>1100)	77	23
Mean (ii)	72	28
Mean, i + ii	63	37

The superiority of liver scanning is perhaps explained by the fact that an abscess on a colloid liver scan actually occupies only 25% of the cold area detected, the remainder being occupied by surrounding inflammation, as judged by blood-pool scan and by angiography (1, 11, 74, 75). This may account for the disproportionate decrease in liver size after aspiration of a small abscess.

Liver scan is also useful in determining resolution of an abscess (7–9, 16, 19, 33). Serial scans have shown that most amebic abscesses heal gradually over two to four months. Resolution time may occasionally extend up to one year (7). Cohen (76) reported a case that showed a cold area on colloid scan $2^1/_2$ years after treatment of the abscess. Resolution does not seem to depend only on size (7, 16). Whether it also depends on medical or surgical treatment has not been settled. Some observers maintain that surgical drainage does not hasten resolution (7, 16); our experience indicates that surgical drainage is certainly indicated in very large abscesses, in multiple abscesses, in toxic, jaundiced patients, and in superficial abscesses to avoid perforation and further complications.

Although the consensus seems to be that liver scan is the most useful procedure for the diagnosis of amebic abscess of the liver, abscesses usually appear as a cold filling defect on a scan and such defects have multiple causes (21). Amebic abscess, cirrhosis with regenerating nodule or hepatoma, and metastatic lesions in the liver together accounted for 81% of the space-occupying lesions in our series of 1,225 scans. It is important to differentiate these (see Table V).

TABLE V

Scan Differentiation of Three Common Space-Occupying Lesions (81% of SOLS in 1,225 Scans)

	Amebic abscess	Cirrhosis with regenerating nodule/hepatoma	Metastatic lesions
Liver size	large	small or normal	large
Isotope uptake	patchy	coarsely patchy and disorganized	normal
No. of lesions	usually single	single or multiple	usually multiple
Spleen size	normal or large	large	normal
Bone marrow uptake	normal	increased	normal

Clinically, in hepatic amebiasis, the patient is often toxic and febrile; the liver is very tender, with intercostal tenderness. Clinical findings are important in interpreting a scan. Further differentiation of the cold focal liver defects can also be made by dynamic studies (13) and by angiographic studies.

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Submitted for publication January 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Phlegmonous Gastritis: Report of a Case

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Abstract

A case of phlegmonous gastritis in an 80-year-old woman is reported. The patient experienced a sudden onset of abdominal pain, fever, nausea, and vomiting. Her death was rapid. Subsequently, hemolytic streptococcus was cultured from her blood. At autopsy, the distal stomach showed a markedly thickened submucosa. Microscopically, polymorphonuclear leukocytes expanded the submucosa, extending into the muscularis propria. Phlegmonous gastritis should be included in the differential diagnosis of an acute abdomen, especially with a concurrent streptococcal infection. Prompt recognition and treatment of this condition are essential.

Phlegmonous gastritis is a distinct clinicopathologic entity characterized by acute inflammation of the gastric wall (1–8). Although often associated with a streptococcal infection, other clinical signs are nonspecific, and without prompt treatment, mortality is high (1–8). Approximately 400 cases of phlegmonous gastritis have been reported, the majority in the pre-antibiotic era. However, the true incidence may be much higher, masked by the number of cases that go unrecognized without a gastrectomy or autopsy specimen. We report a case of an 80-year-old woman to emphasize the importance of an awareness of this entity.

Case Report

An 80-year-old woman was admitted with a two-day history of nausea and vomiting associated with mild stomach cramps. Her medical history was notable for inoperable triple vessel coronary artery disease.

The patient was a confused, slightly obese, white woman with temperature of 105.8°F, blood pressure 100/60. Left upper quadrant guarding was present. Initial laboratory data included white cell count of 2,900 with subsequent elevation to 9,800. Serum amylase was within normal limits. Chest x-ray and urinalysis were unremarkable.

Attempts to delineate a specific site of infection included cultures of sputum and urine and removal of a vaginal pessary. No source was apparent but antibiotics were administered. The etiology of the left upper quadrant pain was unclear and several diagnoses were entertained: mesenteric thrombosis or a ruptured diverticulum, or perhaps pancreatitis, despite the normal serum amylase.

Peritoneal irrigation revealed numerous white blood cells and Gram-positive cocci. Green, bilious material was removed from the stomach via nasogastric tube. Hydration improved the patient's mental status but she experienced continuing hypotension, developed respiratory difficulties, and died 26 hours after admission.

Subsequently, antemortem blood cultures grew beta hemolytic streptococcus, Group A.

At autopsy, the peritoneal cavity contained a minimal amount of clear fluid. The serosal surfaces were smooth and glistening. The gastric mucosa was intact except for a small area of contraction on the posterior wall approximately 3 cm from the pyloric ring. The gastric wall became progressively thicker distally, returning to normal dimensions at the pylorus (Fig. 1). Grossly, the increased thickness was due to a soft, widened, gray submucosa. Microscopically, polymorphonuclear leukocytes expanded the submucosa without mucosal involvement (Figs. 2, 3). The inflammatory process dissected through the muscularis propria with focal extension to the serosa (Fig. 4). Gram stains revealed Gram-positive cocci.

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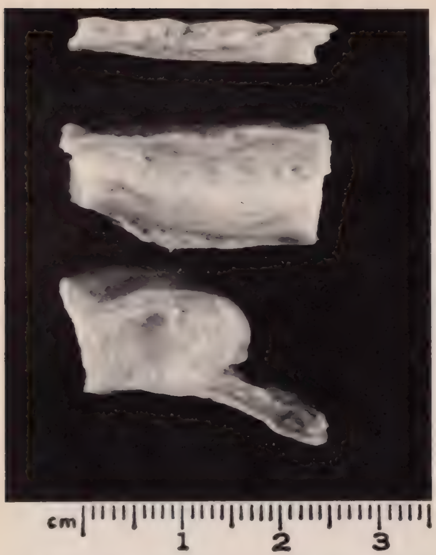

FIG. 1. Section of fundus (top) of normal thickness contrasts with markedly thickened submucosa and muscularis propria in antrum (middle) and pylorus (bottom); duodenum dramatically reverts to normal thickness.

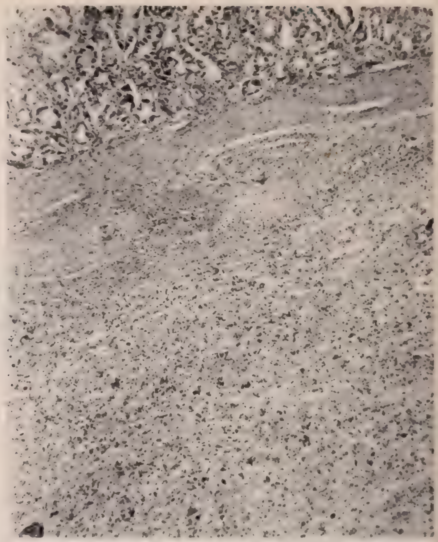

FIG. 2. Intact mucosa and muscularis mucosae overlie submucosa infiltrated by polymorphonuclear leukocytes (H&E ×48).

Discussion

Phlegmonous gastritis has been reported as an entity in the literature for many years; its original description is attributed to Galen (6). Other terms, including suppurative gastritis and gastric abscess, have been used to describe this process. Because of its low incidence, most of the literature consists of isolated case reports and reviews attempting to define clinical and pathologic characteristics. Sundberg in 1919 collected 215 cases (1); Eliason and Murray Wright added a series of 31 cases in 1938 (2). Miller et al in 1975 reviewed a further 23 cases (6), and other small series have also been reported (3–5, 7).

Clinically, patients have epigastric pain, severe nausea, and vomiting. Fever and leukocytosis may be observed initially or may develop. Examination reveals epigastric tenderness, often with signs of peritonitis. Normal serum amylase may distinguish phlegmonous gastritis from pancreatitis (6). Radiographic findings are usually nonspecific (6). Upper gastrointestinal series may show a dilated stomach with edematous folds (6) or apparent displacement of the stomach by an intramural or extrinsic mass (7). Tomography

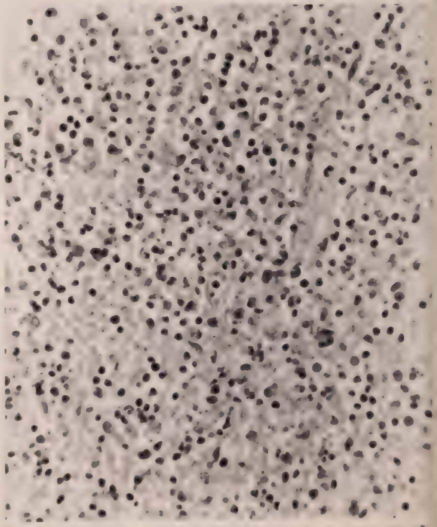

FIG. 3. Polymorphonuclear leukocytes in the submucosa (H&E ×240).

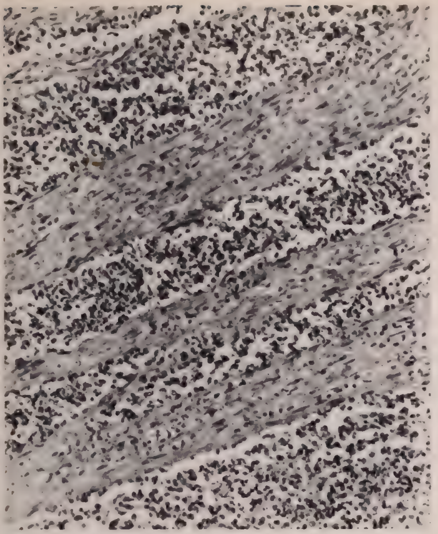

FIG. 4. Acute inflammation separating muscle bundles in the muscularis propria (H&E ×120).

and celiac angiography have been used to document mural thickening or an intramural process (7, 8).

Recently, phlegmonous gastritis has been diagnosed using tissue obtained by endoscopic snare biopsy (9).

Associated bacterial infections have been noted; streptococcus is most commonly isolated. Positive cultures of the gastric wall, blood, urine, tonsils, ascitic fluid, or cerebrospinal fluid have been reported, streptococcus being documented in 45%–84% of cases (2, 6). *Pneumococcus, Staphylococcus, Bacillus coli,* and *Proteus vulgaris* have also been implicated (5).

Pre-existing gastric pathology may be a factor; associated ulcers, carcinoma, or alcoholic gastritis were reported in 42% of patients in one series (2). Direct invasion of a damaged mucosa by organisms has been suggested as a pathogenetic pathway (2, 6). However, in some patients, no previous alteration of the gastric mucosa is demonstrable and the mucosa appears intact. Hematogenous dissemination of organisms from a distant site of infection may also contribute (2, 4–6).

The disease is characterized by a thickened gastric wall. Although usually limited to the distal third (6), the process may involve the entire stomach. However, extension beyond the cardia or pylorus is rare; cessation is often abrupt at the pylorus. Some authors include localized gastric abscess as a chronic form of phlegmonous gastritis, although these instances constitute only a small percentage of cases (7).

Acute inflammation and abscess formation dramatically widen the submucosa, grossly visible as a thick gray band. Extension into the mucosa is rare but the inflammatory process may infiltrate the muscularis propria and serosa and cause local or extensive peritonitis (2, 4–6). Organisms may be demonstrable.

Mortality is high, in earlier reports up to 84% (2), usually within a few days (2, 4–6). However, aggressive treatment by total or partial gastrectomy and antibiotics improves the outlook (2, 6).

In the case presented, the patient died within 26 hours of admission without antemortem results of bacteriological culture. Diagnosis was made at autopsy by the characteristic finding of acute inflammation in the distal third of the stomach. The patient's presentation and course suggested phlegmonous gastritis; the fatal progression would probably not have been altered even had the diagnosis been established, because surgery would have been a great risk in this patient with severe heart disease.

Prompt recognition and treatment of this condition are essential. Phlegmonous gastritis should be included in the differential diagnosis of an acute abdomen, especially with a concurrent streptococcal infection. Endoscopic biopsy may be of value in establishing the diagnosis. In addition to improving the prognosis of these patients, awareness of phlegmonous gastritis as a clinicopathologic entity may increase the available data, further elucidating the pathogenesis and course of this disease.

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Submitted for publication September 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Repair of Rectovaginal Fistula in Crohn's Disease by Rectal Mucosal Advancement Flap

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Abstract

Successful primary repair of rectovaginal fistula in the presence of active Crohn's disease of the colon is presented. Many factors are important for a successful outcome, including proper technique, gentle handling of tissue, meticulous hemostasis, and a well-nourished patient; however, the most important factor appears to be minimal involvement of the anorectum with the disease process. The presence of a rectovaginal fistula in a patient with active Crohn's colitis does not automatically mean that the rectum should be sacrificed. Thus, it may be worthwhile to attempt repair, preferably from the rectal side, before performing rectal excision and permanent ileostomy.

Primary closures of rectovaginal fistulae in Crohn's disease have generally not been successful. The notoriously poor healing of involved rectal and anal tissue is a significant problem. Success may be possible in rare cases with minimal rectal involvement. This report demonstrates such a case, lending support to the trend of rectal preservation in the presence of inflammatory bowel disease, thus avoiding the complications of rectal excision as well as the physical and emotional problems associated with a permanent ileostomy.

Case Report

A 52-year-old white woman was admitted to the medical service in April 1981 with bipedal edema of one week's duration. Two years before, the patient had been diagnosed as having ulcerative colitis and had been treated with sulfasalazine (Azulfidine). Barium enema was performed; findings were consistent with Crohn's colitis with minimal rectal involvement. While in the hospital, the patient developed crampy upper abdominal pain accompanied by nausea, vomiting, and obstipation; she did not mention any urological or gynecological symptoms. Pain increased in severity over 12 hours of observation and then lessened. Physical examination revealed a soft abdomen with diffuse tenderness, greatest in the right lower quadrant, and hypoactive bowel sounds. The hematocrit was 38%; electrolytes and BUN were within normal limits. Leukocyte count was 21,000 per mm. The surgical diagnosis was acute surgical abdomen secondary to perforated viscus.

The patient was rehydrated; intravenous clindamycin (Cleocin) and gentamycin was begun. Sigmoidoscopy to 20 cm revealed a grossly normal mucosa with pus at the upper level of the scope. Exploration of the abdomen revealed copious free intraperitoneal pus and a dilated colon. A subtotal colectomy with end ileostomy and mucous fistula was performed. Pathologic examination revealed granulomatous colitis with abscess formation. The postoperative course was uneventful, and the patient was discharged on the thirteenth postoperative day. The patient was placed on 40 units of ACTH intramuscularly every fourth day.

One month following discharge, the patient was rehospitalized for observation after spontaneously draining an abscess through the inferior aspect of the abdominal incision. She was afebrile with a normal leukocyte count. Sonography failed to demonstrate any additional intra-abdominal collections, and the patient was discharged after three days.

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The patient was readmitted in August 1981 for reanastomosis of the terminal ileum to the rectum. She was placed in Lloyd-Davis stirrups and prepared for E.E.A. anastomosis. Injection of povadone iodine solution into the rectum was followed by egress through a previously unsuspected rectovaginal fistula. The procedure was cancelled in order to discuss with the patient and her family the small likelihood of success of repair of the fistula. Further discussion with the patient elicited a two-year history of persistent vaginal discharge, which the patient's gynecologist had been unable to resolve.

The patient was returned to the operating room and repair via rectal mucosal advancement flap technique was performed (1–3).

Procedure

The operation begins with a curved incision involving one-third the circumference of the anal verge along the anterior surface (Fig. 1). A flap of anal mucosa is elevated and continued 2 cm past the fistula opening (Fig. 1b). The segment of the mucosal flap distal to the fistula is transected (Fig. 1c) and the new edge sutured to the anal verge (Fig. 1d,e). One or two sutures of vicryl are used to close the intraseptal portion of the fistula. To complete the procedure, vaginal and rectal packs of vasilinized gauze are inserted.

Ordinarily constipation is deliberately induced for 3-4 days prior to the procedure; however, since this patient already had an ileostomy, this step was unnecessary. The patient was again placed on ACTH; postoperative course was uneventful. Pathologic examination of the fistulous tract revealed acute and chronic inflammation and fibrosis; no granulomas were identified. In September 1981, the ileostomy was taken down and the terminal ileum reanastomosed to the rectum. After eighteen months, the rectovaginal fistula has not recurred and healing appears complete. Diarrhea has not been a problem.

Discussion

The incidence of perianal disorders in patients with Crohn's disease ranges from 25% to 50% (4). Perianal complications are more common with Crohn's colitis and ileocolitis than with granulomatous ileitis. From 3.6% to 23% of the perianal lesions in patients with Crohn's colitis are rectovaginal fistulae. The majority of patients with rectovaginal fistulae complicating Crohn's disease have advanced transmural disease of the rectum (4–7).

The medical management of rectovaginal fistulae involves control of the intestinal disorder by low-residue diet, steroids, sulfasalazine, and intravenous hyperalimentation. Surgical repair of the rectovaginal fistulae of Crohn's disease should be limited to those that are both refractory to medical therapy and very troublesome to the patient. The likelihood of success in the surgical management of this problem must be considered small at best. Givel et al had only one success out of 13 patients with rectovaginal fistulae secondary to Crohn's disease (8). Faulkner and Muldoon had one success in 15 patients with the same problem, 11 requiring abdominoperineal resection and the rest undergoing diversion of the fecal stream without excision of the rectum (9).

Of the operative procedures that may be performed for this condition, abdominoperineal resection is considered by many to be the procedure of choice (4). Fecal diversion, with or without resection of the diseased bowel, allows the fistula to remain open but usually renders it asymptomatic. Proctocolectomy or rectal excision alone is indicated if there is clinical disease of the bowel adjacent to the fistula (10). Closure of the fistula is possible only when the rectum is minimally involved and intestinal disease is in remission (4).

A trend toward rectal preservation has evolved for several reasons. Less extensive resection results in less operative trauma and allows the possibility of a later reanastomosis if medical therapy is successful. There is a significant incidence of perineal wound complications after an abdominoperineal resection in patients with Crohn's disease (9). Hellers et al (6) note that 60% of patients with Crohn's ileitis or ileocolitis heal after perianal surgery; only 15% of those with colitis will heal primarily. Fecal diversion alone does not appear to improve the healing rate (11). There is some disagreement as to whether resection of the proximal diseased bowel improves perianal wound healing (11, 12). Sohn et al (13) claim sulfasalazine has a beneficial effect when given for two weeks preoperatively and until all wounds are healed.

The technique of anterior rectal wall advancement has been described for the repair of low rectovaginal fistulas (3, 14, 15). It has generally not been recommended for patients with inflammatory bowel disease. The excellent result in our patient may be attributed in part to the prior excision of the diseased bowel, the presence of a diverting ileostomy, and the use of ACTH, but mainly to minimal involvement of the rectum. This case report demonstrates the feasibility of rectal preservation and restoration of normal bowel function in the Crohn's disease patient with a rectovaginal fistula.

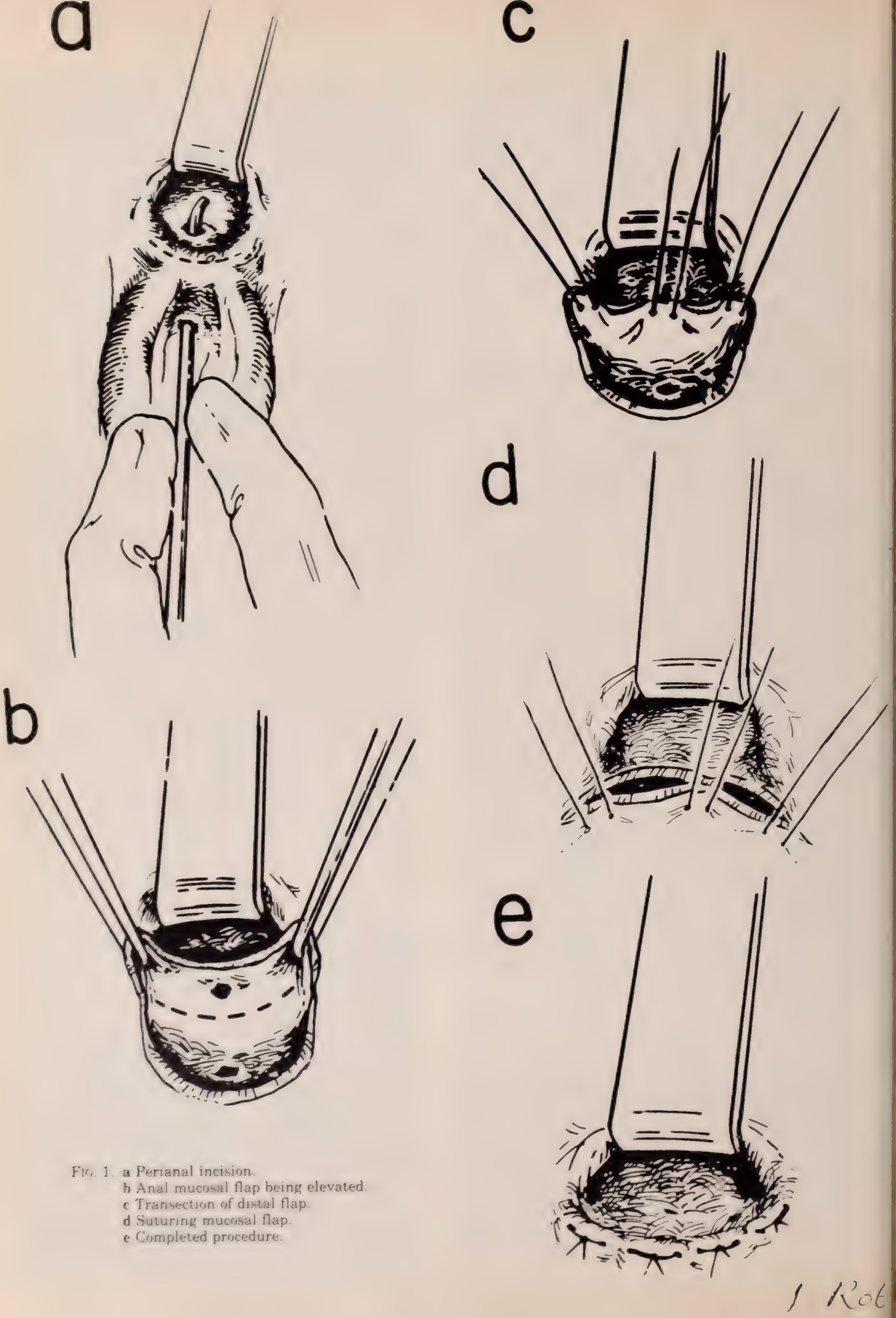

FIG. 1. a Perianal incision.
b Anal mucosal flap being elevated.
c Transection of distal flap.
d Suturing mucosal flap.
e Completed procedure.

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Submitted for publication January 1983.

The Mount Sinai Journal of Medicine
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Non-Hodgkin's Lymphoma of the Pancreas Producing Acute Pancreatitis and Pancreatic Abscess

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Abstract

A case of non-Hodgkin's lymphoma producing pancreatic abscess is described. Although this cause of pancreatic abscess is previously unreported, the application of basic principles of diagnosis and treatment resulted in patient survival.

It is well recognized that adenocarcinoma of the pancreas or ampulla of Vater may initially appear as acute pancreatitis and pancreatic abscess. However, in the English literature non-Hodgkin's lymphoma has not been reported to cause this disease entity. Such a case is described with a brief review of the literature.

Case Report

An acutely ill 75-year-old man in marked distress was admitted to the hospital with a diagnosis of acute pancreatitis. The patient had had a prior right cerebrovascular accident with residual left hemiparesis and mild chronic heart failure. Several years before, cholelithiasis had been documented. On admission, blood pressure was 130/80, pulse 120 beats per minute, temperature 99°F. The patient was anicteric; the abdomen was diffusely tender with guarding in the upper quadrants. Rectal examination revealed hemoccult negative stool. Chest x-ray showed old interstitial fibrosis; abdominal films revealed no pneumoperitoneum, evidence of obstruction, or retroperitoneal air or fluid. Laboratory studies yielded the following values: hemoglobin, 18 gm%; white blood cell count, 9,600 cells/cc; bilirubin, 3.5 mg/ml; SGOT, 300 IU; alkaline phosphatase, 200 units; amylase, 1,000 Somogyi units. Serum calcium level was initially normal.

In spite of adequate hydration, central venous pressure monitoring, intravenous antibiotics, and cimetidine, the patient's condition deteriorated: elevation of temperature to 101°F, white blood cell count rising to 31,000 cells/cc and amylase to 1,560 Somogyi units. Serum calcium fell to 5.2 mg%. Because of the poor prognostic signs, peritoneal dialysis was instituted for 36 hours. During this period endotracheal intubation was necessary because of acute pulmonary failure. The patient was begun on intravenous hyperalimentation. Twenty-four hours after the dialysis was discontinued the patient again began to decompensate, with falling blood pressure, serum calcium, and urinary output as well as rising white blood cell count, serum amylase, and temperature. Peritoneal dialysis was reinstituted for 36 hours. An abdominal sonogram at this point did not reveal a pseudocyst or pancreatic abscess. The patient again improved and 3 days after discontinuing dialysis extubation was accomplished.

At this point the patient had been hospitalized 14 days. Repeat sonogram was unremarkable. However, 5 days later the patient became febrile to 103°F. All central venous lines were changed and penicillin and chloramphenicol therapy was started. The patient became lethargic with temperatures rising to 105°F. An abdominal CT scan revealed a possible pancreatic abscess within the substance of the gland (Fig. 1). In view of the patient's deteriorating condition, exploratory laparotomy was performed on the 22nd hospital day. At surgery 200 cc of purulent material was drained from the pancreatic bed and the entire

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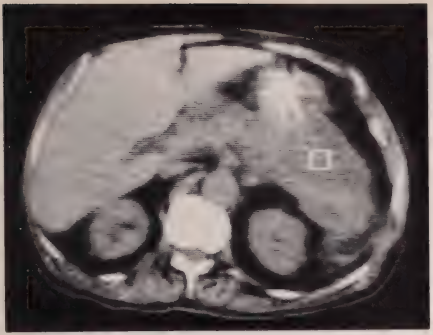

FIG. 1. CT scan, pancreatic abscess.

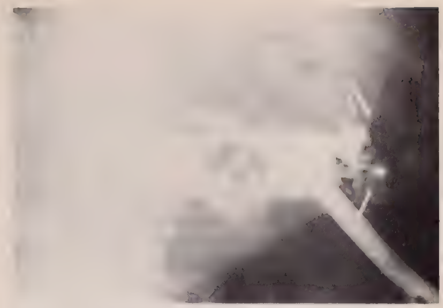

FIG. 3. Fistulogram revealing large residual abscess cavity.

pancreas and the left upper retroperitoneum were debrided of necrotic material.

Large sump drains were left in the abscess cavity and tube gastrostomy was performed. The material debrided from the pancreas was reported as non-Hodgkin's lymphoma (Fig. 2).

Two weeks postoperatively the patient's condition was markedly improved; extubation was carried out successfully and daily irrigation of the abscess bed was performed. A fistulogram at this point (Fig. 3) revealed a large cavity. One month after surgery, oral feedings were begun, without incident. Over the next two months the abcess cavity shrank to a small sinus, and all drains were removed, with rapid closure of the fistula. The patient was transferred to an extended care facility; one year after the operation he was doing well without radiotherapy or chemotherapy. These therapies were not used by decision of the patient and his family.

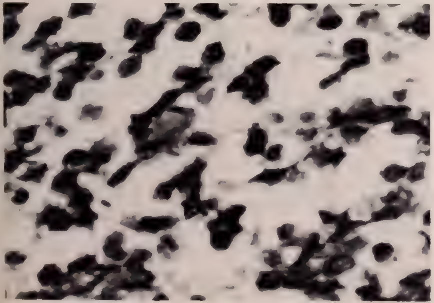

FIG. 2. Photomicrograph of abscess material: "Non-Hodgkin's lymphoma."

Discussion

Inflammatory and malignant diseases produce significantly higher morbidity and mortality in the pancreas than in other parts of the intestinal tract. The most devastating of these diseases is pancreatic abscess, originally described by Fitz (1) in 1887. Since that time, reports on large series (2–4) have described the signs and symptoms, bacteriology, pathophysiology, and therapy of pancreatic abscesses.

A pancreatic abscess is an infected pseudocyst secondary to fortuitous bacterial invasion of enzymatically autodigested areas of pancreas and surrounding adipose tissue (5). Abscess formation may be associated with an episode of acute pancreatitis of any origin (6). Abdominal pain radiating to the back may be a predominant symptom or completely absent; wide fluctuations in temperature and abdominal tenderness are usual. A rising white blood cell count is frequent, but a persistently elevated serum amylase level occurs only in a minority of cases. Positive blood cultures are found in approximately 50% of patients. Radiographically, a gas-filled soft-tissue collection in the area of the pancreas in a septic patient is suggestive of pancreatic abscess. The development of signs or symptoms of toxicity 10 to 14 days following an episode of acute pancreatitis should suggest the possibility of a pancreatic abscess. Once a diagnosis of pancreatic abscess is entertained, urgent and accurate diagnosis is imperative. Before computerized axial tomography, ultrasound was the procedure of choice. However, ultrasound in the area of the pancreas can only identify a fluid-filled collection indistinguishable from a pseudocyst or other reactive fluid loculation. As in the patient reported, many patients with an abscess do not form well-defined abscess cavities; the ultrasound results may therefore be normal. The presence of gas within the parenchyma of the pancreas on CT scan is virtually pathognomonic of pancreatic abscess. Therefore, CT scan is currently considered the diagnostic mode of choice for patients with suspected pancreatic abscess (7).

When no causal factor can be identified for acute pancreatitis and its complications, a primary cancer obstructing or infiltrating the pancreas must always be considered (8). Although it is well recognized that acute pancreatitis may occur with tumors of the periampullary region or in the head of the pancreas (9), very few authors mention the association between malignancy of the pancreas and pancreatic abscess (3). In most reported cases the time that elapses between the initial episode of pancreatitis and definitive diagnosis of the malignant condition is significant (10). Gambill reported histologically significant pancreatitis in 26 (10%) of 255 patients with pancreatic or ampullary carcinoma, the pancreatitis resulting in a significant delay in the diagnosis of malignancy (11).

The occurrence of pancreatic abscess secondary to carcinoma may be better understood if the experimental work of Pour et al (12) is appreciated. They observed in human and animal models that pancreatic neoplasias were capable of producing vascular thrombosis and fat necrosis, certainly associated with acute pancreatitis and pancreatic abscess formation.

Whether non-Hodgkin's lymphoma causes pancreatitis and pancreatic abscess by the same mechanism is purely conjectural. Large reviews of patients with intraabdominal non-Hodgkin's lymphoma do not mention pancreatic involvement. Kim and Dorfman (13) reported 84 cases of non-Hodgkin's lymphoma; 51 (61%) cases involved one or more sites below the diaphragm. No mention was made of pancreatic invasion; however, tumors in the spleen, splenic hilar nodes, and paraaortic and mesenteric nodes were described. Direct invasion of involved nodes into the pancreas with ductal obstruction may represent the mechanism by which this malignancy caused acute pancreatitis and pancreatic abscess.

Pancreatic abscesses develop in a reported range of 2% to 8% of cases of pancreatitis, usually in the more severe cases following inappropriately early operation or feeding. Whether the pancreatic abscess is malignant or benign in etiology, the treatment remains the same: adequate drainage, antibiotics, cardiopulmonary support, and parenteral nutrition (Fig. 4).

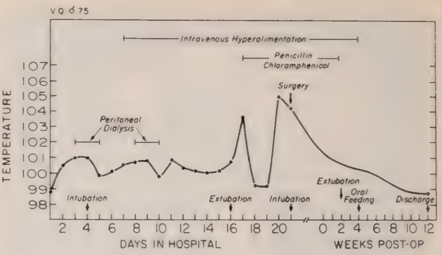

FIG. 4. Patient's hospital course with treatment.

A pancreatic abscess is usually not a single loculus of pus; rather, there tends to be a widespread necrotizing process that involves the pancreas, retroperitoneum, and lesser sac. There may be multiple areas of necrotic, infected tissue, all of which must be debrided and drained. The lesser sac must be widely opened through the gastrocolic omentum and the entire retroperitoneum explored (14). Sump drainage is preferable to simple Penrose drains. Vankemmel (16) has recommended, after standard surgical measures, the placement of catheters for continuous lavage of the abscess bed similar to peritoneal lavage for acute pancreatitis (15). The resulting fistulous tract almost uniformly closes spontaneously, as it did in our case. Reoperation is often necessary in the face of a pancreatic abscess (usually within 3 to 5 days of the original surgery) if the patient fails to improve, or again begins to deteriorate.

The use of antibiotics, debatable in acute pancreatitis (17, 18), is absolutely indicated in pancreatic abscess. A broad-spectrum antibiotic is perferred because of the range of enteric organisms that have been identified: *Escherichia coli, Enterobacter, Proteus, Pseudomonas, Staphylococcus aureus, Klebsiella,* and *Serratia marsescens* (all identified in the case reported here).

Cardiopulmonary support is extremely important. Adequate fluid resuscitation, a Swan-Ganz catheter, pulmonary toilet and assisted ventilation, blood and blood-product replacement, calcium monitoring and supplementation, and acid-base balance correction all play a role in successfully treating the patient. As indicated by Ranson (19), Jacobs (20), and Satiani (21) in respect to acute pancreatitis, certain factors warn of poor outcome in pancreatic abscess. These include respiratory complications, shock, hemorrhage, and recurrent abscess formation. These complications must be recognized early and treated aggressively.

Nutritional support of these critically ill patients is essential. In such a complex surgical illness, parenteral nutrition enhances wound healing and preserves maximum ability to resist the infection (22). Intravenous feeding also aids in decreasing pancreatic secretion and aborting the inflammatory process in the pancreatic parenchyma (23).

Although non-Hodgkin's lymphoma has not been described as a malignancy of the pancreas (24), the successful treatment of this unusual case of secondary pancreatic abscess by adequate drainage and supportive measures emphasizes the cardinal rules of therapy of a pancreatic abscess of any etiology.

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Submitted for publication December 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Hyperkalemia-Induced Pseudoinfarction Pattern

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Abstract

A patient with chronic renal failure and documented right coronary artery disease developed hyperkalemia, chest pain, and acute heart failure. There was electrocardiographic evidence of inferior and anterior wall myocardial infarction which was reversible with dialysis. Follow-up studies showed no evidence of acute myocardial infarction, suggesting that hyperkalemia was the cause of the abnormal electrocardiographic patterns. Therefore, in patients with renal failure who have chest pain and electrocardiographic changes compatible with acute myocardial infarction, hyperkalemia must be excluded even when the patient has known coronary artery disease.

A variety of electrocardiographic changes due to hyperkalemia have been described (1, 2). These include peaking of the T waves, intraventricular conduction disturbances, prolongation of the PR interval, widening and loss of amplitude of the P waves, shortening of the QT interval, atrial and ventricular arrhythmias, bundle branch block (3–5), and complete heart block (6, 7).

Several cases of QRS changes simulating myocardial infarction during hyperkalemia have been reported (8–12). We describe here a patient with coronary artery disease, documented by cardiac catheterization, who developed hyperkalemia, chest pain, and heart failure. There was electrocardiographic evidence of inferior and anterior wall myocardial infarction that disappeared immediately after the hyperkalemia was corrected.

Case Report

A 47-year-old woman with diabetes mellitus and end-stage renal disease was admitted to The Mount Sinai Hospital because of pulmonary edema. She had had diabetes requiring insulin since age 18 and had been in hemodialysis for 21 months. However, because of graft thrombosis, femoral dialysis had last been performed three days prior to admission.

She had noted exertional chest pains for the last two years, and had had several hospitalizations for coronary insufficiency without myocardial infarction. Coronary angiography performed seven months prior to admission had revealed significant obstructive disease of the right coronary artery and a normal left coronary arterial system. Subsequently, she had been maintained on Isordil and Inderal with stabilization of her anginal pattern. An electrocardiogram performed one month prior to the current admission to the hospital revealed normal sinus rhythm, left atrial enlargement, and ST segment and T wave changes (Fig. 1). On the evening of the admission, she had an episode of her usual anginal pain, rapidly followed by severe shortness of breath, nausea, diaphoresis, and a choking sensation.

She had been treated for hypothyroidism for the last 10 years with oral thyroid preparation. She had smoked one pack of cigarettes per day for 25 years until 2 years before admission.

In the emergency room, the patient appeared pale, diaphoretic, and in acute respiratory distress. The blood pressure was 150/90 mm Hg, pulse 140 beats per minute, and respirations 30 per minute. There were coarse rales throughout the lungs. The neck veins were fully distended at 90 degrees. A diastolic gallop was heard at the apex. The extremities were slightly cyanotic, with 1+ edema.

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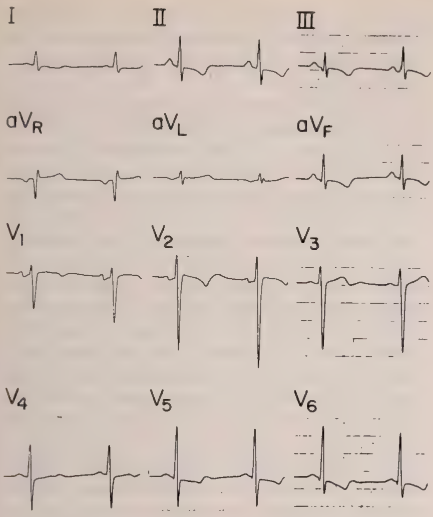

FIG. 1. ECG performed one month prior to described hospitalization showing sinus rhythm, left atrial abnormality, and diffuse ST segment and T wave changes. PR: 0.15; QRS: 0.09; QT: 0.36.

Arterial blood gases showed a pH of 7.02, P_{CO2} of 70, and P_{O2} of 62. The electrocardiogram revealed sinus tachycardia with new QS waves in leads III and aVF (Fig. 2). An acute inferior wall myocardial infarction was assumed to be present and she was treated with intravenous morphine and furosemide, nasal oxygen, rotating tourniquets and phlebotomy of 200 cc, with some improvement in her clinical condition. Another electrocardiogram taken 3 hours later revealed new Q waves in leads V_1–V_4 and marked left axis deviation (Fig. 3). At this point, the serum potassium was reported as 7.7 mg%. Femoral dialysis was promptly initiated and an electrocardiogram following dialysis showed disappearance of all the abnormal Q waves (Fig. 4). The postdialysis serum potassium was 4.1 mEq%. No further electrocardiographic changes occurred during her hospital course, and serial creatine phosphokinase, serum glutamic oxaloacetic transaminase, and lactic dehydrogenase determinations showed no evidence of myocardial necrosis.

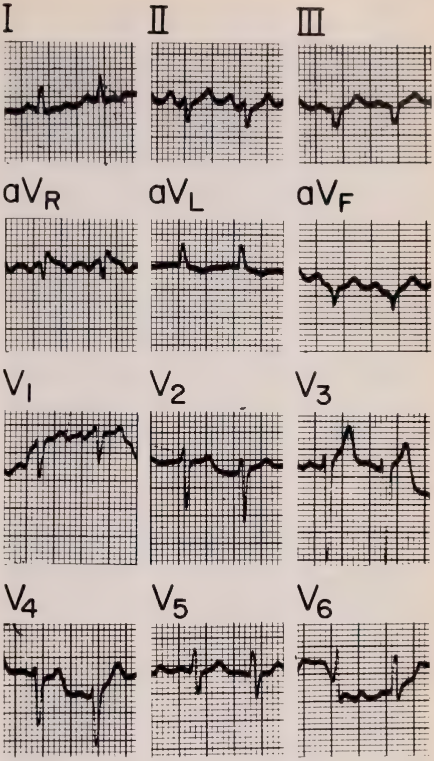

FIG. 2. ECG taken in emergency room the day of admission to the hospital showing sinus tachycardia with heart rate of 140 beats/minute and new QS pattern in leads III and aVF consistent with inferior wall myocardial infarction. PR: 0.14; QRS: 0.10; QT: 0.28.

Discussion

Electrocardiographic patterns simulating those seen in the various stages of the evolution of an acute myocardial infarction have been described during hyperkalemia (8–14). ST segment depression and T wave inversion typical of myocardial ischemia and reversible with the correction of hyperkalemia have been described (8). In those cases, no Q wave development occurred and the clinical settings were not likely to be confused with acute myocardial infarction. On more unusual occasions (9), Q wave formation has been observed transiently during hyperkalemia and in at least one case the Q waves evolved in leads V_1 to V_4 after peaking of the T waves.

Therefore, the electrocardiographic pattern that may be seen during hyperkalemia can mimic that of an acute or of an old myocardial infarction. These electrocardiographic changes may occur during relatively low levels of hyperkalemia and

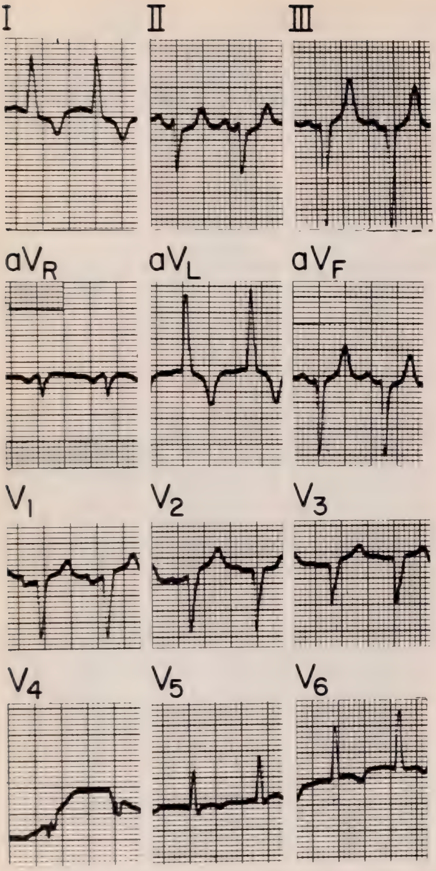

FIG. 3. ECG taken 3 hours after the one in Fig. 2. New Q waves in leads V_1 through V_4; increased QRS voltage in the limb leads and peaking of T waves in inferior leads. PR: 0.13; QRS: 0.11; QT: 0.31.

be absent at higher levels of serum potassium. Moreover, these patterns may occur in patients with coronary artery disease or in patients with normal coronary arteries. In our case, it was initially impossible to suspect that hyperkalemia was the cause of the inferior wall myocardial infarction pattern in the electrocardiogram, given the history of right coronary artery disease, documented by cardiac catheterization, and the clinical presentation with chest pain and heart failure. However, the initial treatment of such patients, with or without myocardial infarction, is the same, because correction of the hyperkalemia by dialysis is essential. Dialysis will permit correction of heart failure and fluid overload at the same time.

Transient abnormal Q waves have been described during hypoglycemia (15), acute pancreatitis (16), shock (17, 18), phosphorus poisoning (19), Prinzmetal's angina (20), cerebrovascular accident (21), and cross-clamping of the aorta (22). Abnormal Q waves that develop with chest pain and later disappear have been observed in patients with angina pectoris (24, 25) and with Prinzmetal's angina (20–26). True transient transmural myocardial ischemia must be suspected in any patient who has new Q waves. Evaluation of left ventricular function by echocardiography or radionuclide angiography during these electrocardiographic changes would clarify the question of whether myocardial ischemia is present.

Hyperkalemia can induce intraventricular conduction disturbances which can cause abnormal Q waves (23). In the case reported here, the first electrocardiographic pattern suggesting an inferior myocardial infarction (Fig. 2) is clearly related to the development of left axis deviation as a result of a new conduction block, possibly a left anterior hemiblock. A diffuse intraventricular

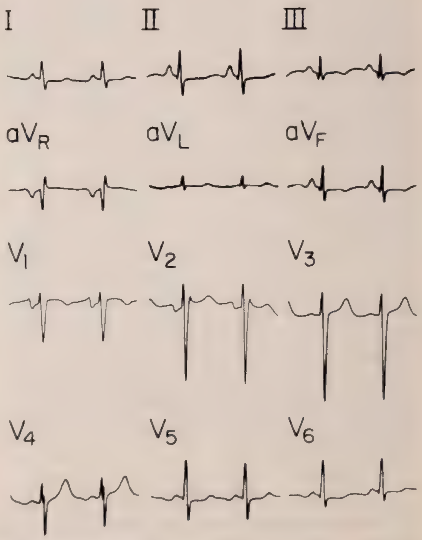

FIG. 4. ECG after hemodialysis demonstrating disappearance of all abnormal Q waves.

conduction disturbance probably explains the electrocardiographic pattern mimicking an anterior myocardial infarction (Fig. 3). When widening of the QRS does not occur during hyperkalemia, the cause of the Q waves is unclear. The initial and terminal portions of the QRS complexes are prolonged during hyperkalemia because of shortened duration of the myocardial action potential and decreased rate of ventricular depolarization (27). These changes are due to a reduced influx of sodium when the resting membrane potential is decreased by rising serum potassium levels (28). Therefore, the temporary loss of action potential induced by hyperkalemia causes pathologic Q waves due to localized alterations in the cell membrane rather than cell death (29). The depression of conduction by hyperkalemia also accounts for transient right or left axis deviation (20), bundle branch block (3–5), and complete heart block (6, 7), which resolve with normalization of serum potassium.

This case illustrates the importance of rapid serum potassium determination in patients with renal failure presenting as acute myocardial infarction, even with known obstructive coronary artery disease and unstable angina pectoris.

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Submitted for publication February 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Management of Extensive Perineal Necrotizing Fasciitis

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Necrotizing fasciitis is a rare infection by nonclostridial mixed bacterial florae, characterized by progressive necrosis of deep and superficial fasciae. Infection originating from or developing around the perineal area is not common, and is notorious for very high morbidity and mortality. (1–3).

In 10 years we treated 33 cases of perineal necrotizing fasciitis, with an overall mortality rate of 36.3% (12/33). Earlier findings that old age (1, 3), diabetes mellitus (1, 3, 4), and delayed medical attention (1, 3–5) are the factors responsible for high death rate in this infection were confirmed in this study. Our increased experience and better understanding of this infection enabled us to improve survival.

Clinical Material and Results

A total of 33 cases of necrotizing fasciitis involving the perineal area were managed at The Mount Sinai Medical Center during the 10 years from September 1971 to August 1981. The 33 cases included 24 males and 9 females. The age range was 15 to 89 years, mean age 59 years. The overall mortality rate was 36.3% (12/33); diabetes mellitus was associated with 39.4% of the cases. The diabetic patients had a much higher mortality rate, 69.2% (9/13), than the 15% (3/20) rate in the nondiabetic group. Diagnosis and treatment was delayed more than 5 days after onset in 22 cases; this group had a high mortality rate of 50% (11/22). However, among the 11 patients who received treatment within less than 4 days after onset, only one death (9%) occurred.

Tests of all the patients revealed mixed infection of gram-negative rods and gram-positive cocci on the smear. The organisms most frequently found on the culture were *Escherichia coli,* enterococcus, anaerobic *Streptococcus,* and bacterioides, in decreasing order. Approximately half of the patients experienced perianal pain, fever, and local swelling at the onset. Two cases developed after ureterolithotomy. Eighty percent of our 33 patients were referred from other hospitals after one or more debridement procedures; most were not adequately debrided. Sixty-six percent of the 33 patients required surgical debridement more than twice and 50% had reconstructive surgery, using skin graft or myocutaneous flaps.

Discussion

"Necrotizing fasciitis" is the preferred descriptive term for various types of soft-tissue infections, regardless of causative organism. Characterized by extensive progressive necrosis of fasciae and cutaneous structures (1), these infections are predominantly caused by mixed gram-negative enteric bacteriae and gram-positive cocci. *E. coli,* the *Pseudomonas* group, hemolytic *Streptococcus,* and *Peptostreptococcus* are frequently isolated from the wounds (1–4).

Gram staining of the wound is important, and is mandatory to rule out gas gangrene in all cases in which it is suspected. Early lesions are tense, shiny, erythematous, tender skin swellings; late lesions are characterized by pleomorphic picture of skin damage with irregular dusky discoloration, blisters, and frank cutaneous necrosis. Fasciae are always necrotic and dark green-gray or brown. Subcutaneous fat is paler than normal, and a small amount of thin, dirty fluid is usually found in the fascia plane. No frank pus is present; gas may or may not be found. Usually, underlying muscles are spared unless enveloping fasciae are involved.

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Systemic toxic symptoms are usually associated with severe lesions and cause high fever and alteration in mentation. Although necrotizing fasciitis is a rare infection, it occurs frequently in the perineal area (1, 2, 7). Pre-existing anal fistula, fissure, trauma, or surgical injury can cause this infection. However, half of the patients in this study had no significant positive history. Extensive lesions in the perineum and adjacent area may present many difficult management problems and are associated with markedly high mortality (1–3). Because the anorectum is surrounded by potential spaces with loose fascial planes, infection usually spreads quickly. Therefore, surprisingly widespread necrosis of perineal tissue with minimal cutaneous manifestation is frequent. Often, initial debridement and subsequent wound care of perineal lesions are compromised because of the anatomical location, and failure in early control of the infection may result.

The high mortality rate in the delayed-treatment group was mainly due to widespread fascial necrosis and concomitant systemic sepsis. Small lesions diagnosed early are usually treated by wide excision and relatively simple local wound care thereafter. However, in extensive fulminating cases, resuscitative measures for septic shock are essential, along with radical wound debridement. The cause of the higher mortality rate in diabetic patients has not been well understood, but fibrin deposition in the capillary and impaired capillary circulation might be a factor in the rapid spread of infection (8).

Close monitoring of hemodynamics and cardiorespiratory supports are mandatory. Hydration, transfusions, and broad-spectrum antibiotics should be started immediately. Cephalosporin, aminoglycosides, and clindamycins are usually the first-line antibiotics for gram-negative bacilli and gram-positive cocci. Specific antibiotics can be replaced when sensitivity test results are available. Hyperbaric oxygenation treatment was not used for nonclostridial necrotizing fasciitis.

The wound debridement should be excisional and radical, with immediate, extensive, and thorough excision of all involved skin, fasciae, and muscles until healthy tissues are exposed. Incision and drainage are absolutely not adequate. Some lesions expand so rapidly that several hours delay of treatment can alter outcome. Early in our experience, we tried to save tissue at the debridement and left any possibly viable lesion in place. However, these lesions became a nidus of continuous spreading infection. Any suspect lesion is better excised than spared, because in almost all cases which developed further spread of infection after initial debridement, the infection came from a lesion not excised. After initial debridement the wound should be checked frequently during the first 24–72 hours. Further debridement is indicated whenever expansion of infection is found (4). Diverting colostomy is an important part of primary surgical treatment to prevent continuous fecal soilage of the perineal wound. Transverse colostomy is preferable, because low abdominal walls are frequently involved by extension of the perineal infection.

The management of an extensive area of wound surface after debridement is the same as in full-thickness burn wound treatment. A thick layer of wet dressing using saline, Betadine, or Dakin's solution (sodium hypochlorite solution 0.5%) gives a comfortable feeling to the patient and minimizes water loss. Half-strength Dakin's solution is good for a *Pseudomonas*-infected surface wound; this solution is not only germicidal but also dissolves necrotic tissues. When Betadine (povidon-iodine, 10%) solution is used, special care should be given because it causes yellow-brown staining of wounds which looks very similar to expanding fasciitis.

Biological dressing with porcine skin (fresh, fresh frozen; Burn Treatment Skin Bank, Phoenix, Arizona 85034) was excellent for the purpose of temporary skin coverage. However, an infected surface with purulent exudate is managed much better with wet dressings before application of biological dressings.

The ultimate goal of treatment is permanent coverage of the skin defect; the sooner the wound is covered, the more complications can be avoided. Aggressive nutritional support and meticulous and diligent wound care promote growth of granulation tissue, and can shorten the time before skin grafting. Either enteral or parenteral feeding at a rate of 40 to 50 cal/kg/day and of adequate protein, 2–3 gm/kg, will produce positive nitrogen balance in patients who are moderately severely catabolic (9).

In addition to hyperalimentation, multiple transfusions and plasma replacement are necessary in the early period when the patient undergoes extensive debridements and surface oozings are still considerable. Throughout the entire course of patient management, adequate levels of analgesia and sedation have to be maintained. Otherwise, ventilatory support, daily wound management, and nursing care cannot be performed adequately. Tracheal suctions, adequate dressing changes, and frequent turning to prevent pressure sores are very important for the patient with an extensive wound area.

Continuous intravenous infusion of thiamylal sodium (Surital) results in excellent anesthesia; it gives oblivion to the continuously suffering patient and manageability to an uncontrollable patient. Although it requires endotracheal intubation for secure airway, respiratory drive remains intact. Severe agitation, continuous suffering, and fighting against ventilatory drive are completely abolished by this technique and the patient sleeps comfortably. When a patient undergoes painful dressing changes and a bedside debridement, a small amount of morphine sulfate or ketamine hydrochloride can be added to obtain adequate analgesia. Using this technique, we were able to perform quite extensive dressing changes and debridements easily at the Intensive Care Unit bedside. No adverse cardiovascular or hepatic symptoms were noticed in the dose range used for this purpose. Another satisfactory method of pain control is continuous intravenous infusion of morphine sulfate. Because this technique does not lead to a dangerously high serum level, respiratory depression is less frequent than in bolus injection technique. Also, analgesia is adequate, onset of tolerance is slow, and weaning or reversal is easy (10).

A major triumph in the management of a large perineal wound is early reconstruction utilizing gracilis myocutaneous flap. It fills any large cavitary defect and covers the surface nicely. This technique shortened hospital stays tremendously. Waiting until granulation tissue fills the large wound cavity not only takes a long time, but can cause functional problems.

Summary

Thirty-three cases of perineal necrotizing fasciitis were treated at The Mount Sinai Medical Center from September 1971 to August 1981 with overall mortality of 36.3%. Delayed surgical intervention, old age, or association with diabetes mellitus were factors responsible for the high death rate in this infection. The mortality rate of 64% during the first 5 years of our experience decreased to 15.7% in the latter 5 years.

Early diagnosis, initial radical excisional debridement, aggressive multisystemic supportive measures, and early wound coverage are essential to reduce mortality.

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Submitted for publication January 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

VATER Association and Unrecognized Bronchopulmonary Foregut Malformation Complicating Anesthesia

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Abstract

A neonate with VATER association accompanied by origin of the right main stem bronchus from the esophagus is reported. The patient died at age ten hours of massive hemorrhage from the upper gastrointestinal tract during induction of anesthesia. Awareness and understanding of this anomaly and its embryologic origin permits its recognition. Repair of the esophageal atresia and tracheo-esophageal fistula must be accompanied by treatment of the bronchopulmonary foregut malformation, if severe morbidity or mortality is to be avoided.

Anesthesia for repair of esophageal atresia with tracheo-esophageal fistula presents many hazards. Although 27% of cases of esophageal atresia with tracheo-esophageal fistula are associated with other anomalies which may affect the neonate's survival (1), these other anomalies are not always diagnosed preoperatively. Thus, the anesthesiologist may be called upon to anesthetize a patient who has additional anomalies of which he is unaware.

The VATER association, described by Quan and Smith (2), constitutes an association of anomalies for which the name is an acronym: vertebral defects, anal atresia, tracheo-esophageal fistula and esophageal atresia, radial dysplasia, and renal defects. Temtamy and Miller (3) suggested extending the definition of VATER association to include vascular and cardiac anomalies when they found an 80% incidence of these in their series. Pulmonary sequestration with gastrointestinal communication is a very rare anomaly (4, 5), and Gerle et al (6) suggested the term "congenital bronchopulmonary foregut malformations" for these anomalies because lung and esophagus both develop from primitive foregut.

A neonate with VATER association was anesthetized for repair of esophageal atresia with tracheo-esophageal fistula, but suffered massive upper gastrointestinal hemorrhage after induction of anesthesia and died before surgery was undertaken. Postmortem examination revealed a large tracheo-esophageal fistula and an anomalous origin of the right main stem bronchus from the esophagus.

Report of a Case

A 2850-gram male infant was vaginally delivered after term pregnancy to a 25-year-old woman with negative serologic findings, gravida 2, para 1, abortus 0. Ten days before delivery she was admitted to hospital with pre-eclampsia, prompting treatment with bed rest and oral phenobarbital. There was no history of illness or drug ingestion during early pregnancy. The infant was born after spontaneous rupture of membranes and pitocin-augmented labor. Apgar scores at one and five minutes were 5 and 7, respectively. The infant was cyanotic and in respiratory distress with marked substernal and retrosternal retraction.

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Breath sounds were diminished over the right hemithorax and chest x-ray revealed haziness of the right lung field (Fig. 1). A diagnosis of VATER association was made based upon the following: (a) esophageal atresia with tracheo-esophageal fistula; (b) low type imperforate anus; (c) two hemivertebrae; (d) suspected dextrocardia. Capillary blood gases on F_{IO_2} 0.84 administered by oxyhood were: pH 7.22, P_{CO_2} 57 torr, P_{O_2} 87 torr. Continued treatment with oxygen and oropharyngeal suction produced some improvement of cyanosis and respiratory distress. Penicillin 150,000 units and Gentamycin 7.5 mg were administered intravenously. A nasogastric tube was passed into the upper esophageal pouch and connected to continuous suction.

Ten hours after birth, the patient was brought to the operating room, where he was acyanotic, breathing spontaneously in an enriched oxygen environment with heart rate of 140/minute. A thermal blanket and an overhead heater maintained body temperature at 37°C. Heartbeat and electrocardiogram were monitored continuously and an intravenous infusion was secured. Oxygen was administered for ten minutes with a nonrebreathing circuit with humidification. Awake endotracheal intubation was attempted with a size 3 tube with stylet. The tube was passed between the vocal cords, but severe retrosternal retraction developed and breath sounds were inaudible. The endotracheal tube was suctioned, producing gastric contents. The tube was removed and reinserted with similar results. On the third intubation, there was no retrosternal retraction and breath sounds were audible, although softer on the right side than on the left. Placement of the tube was verified. No cyanosis or bradycardia occurred. The patient was allowed to spontaneously breathe nitrous oxide:oxygen 3:3 with 1% halothane.

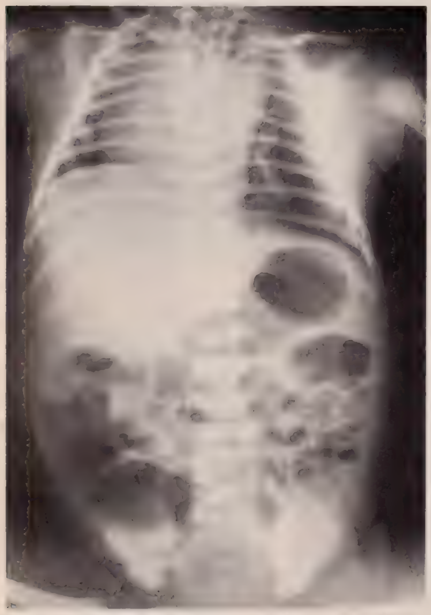
Fig. 1 Chest x-ray: anterior-posterior view, preoperatively.

After ten minutes the patient was placed in the left lateral decubitus position; the result was cyanosis and cessation of respiration. Immediately, he was returned to the supine position. Profuse hemorrhage appeared from the endotracheal tube. Manual ventilation was impossible; pallor and bradycardia followed and suctioning had little effect. Sodium bicarbonate 3mEq., atropine 0.04 mg, lasix 3 mg, and 50 ml of packed red blood cells were administered. External cardiac massage was initiated, but resuscitation was unsuccessful. After 20 minutes the patient was pronounced dead, but events leading to the cause of death were unknown. Immediate postmortem chest x-ray revealed neither pneumothorax nor mediastinal emphysema.

Postmortem findings included: esophageal atresia with blind upper pouch and lower tracheo-esophageal fistula; agenesis of right main stem bronchus, pulmonary artery, and pulmonary vein with origin of bronchial communication to right lung from distal esophagus; systemic vascular supply to right lung (pulmonary sequestration); ruptured esophageal varices with 100 ml of blood in stomach; pulmonary and mediastinal emphysema; bilateral pulmonary atelectasis; unilobed left lung; hypoplastic and unilobed right lung (Fig. 2).

Discussion

In the course of anesthesia and surgery there are numerous risks from esophageal atresia and tracheo-esophageal fistula. Risks are compounded when an undiagnosed anomaly interferes with adequate ventilation during the procedure. In the case reported here, obviously the first two attempts at endotracheal intubation resulted in intubation of the tracheo-esophageal fistula (Fig. 3). After the third attempt, the tube was positioned proximal to the fistula, but the atretic right bronchus prevented direct ventilation of the right lung. Whatever air reached that lung did so

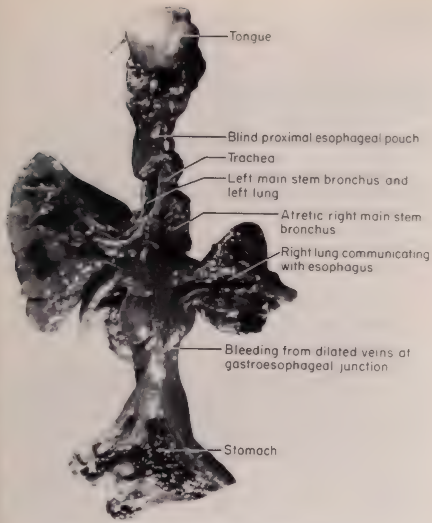
Tongue
Blind proximal esophageal pouch
Trachea
Left main stem bronchus and left lung
Atretic right main stem bronchus
Right lung communicating with esophagus
Bleeding from dilated veins at gastroesophageal junction
Stomach

FIG. 2. Postmortem specimen: posterior view.

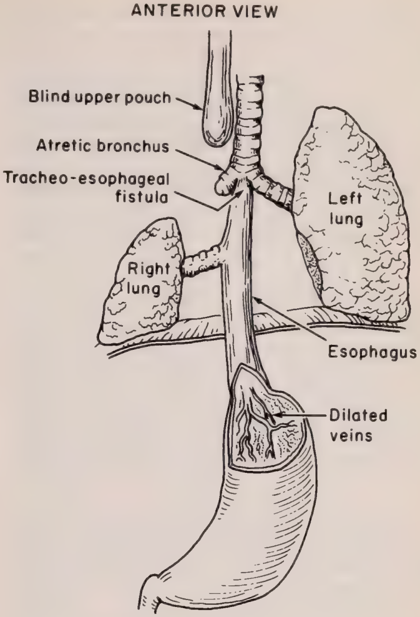
ANTERIOR VIEW
Blind upper pouch
Atretic bronchus
Tracheo-esophageal fistula
Left lung
Right lung
Esophagus
Dilated veins

FIG. 3. Schematic representation of anatomic pathology.

through the tracheo-esophageal fistula and the right lung's communication with the distal esophagus. Upon positioning the patient in the left lateral decubitus position, the tube moved into the fistula, obstructing ventilation of the left lung. The unrecognized occurrence of esophageal atresia and tracheo-esophageal fistula with bronchopulmonary foregut malformation complicated appropriate assessment of the child's ventilatory status and necessitated manipulation of the endotracheal tube. Efforts to overcome the malpositioning of the endotracheal tube, and possibly suctioning through the tube during the first two intubation attempts, may have caused rupture of esophagogastric varices leading to exsanguination.

Congenital bronchopulmonary foregut malformations are rare defects (7, 8). They encompass a spectrum of findings which include intralobar and extralobar sequestration with or without communication with the gastrointestinal tract, foregut duplication cysts, and esophageal diverticula. The occurrence of a congenital bronchopulmonary foregut malformation in a patient with esophageal atresia and tracheo-esophageal fistula is extremely rare (4, 5), developing during differentiation of the tracheobronchial tree and the esophagus from the laryngotracheal ridge.

Although age at diagnosis of bronchopulmonary foregut malformation has ranged from one day to 48 years (4–8), the association of esophageal atresia with tracheo-esophageal fistula and bronchopulmonary foregut malformation probably precludes preoperative diagnosis. Clinical signs and symptoms include chronic cough often related to feeding, recurrent pneumonia, and respiratory distress. The esophagogram has been the most useful diagnostic investigation (8). A hemodynamic study with a radionuclide is a useful noninvasive method to demonstrate a perfusion defect, highly suggestive of a bronchopulmonary foregut malformation (9, 10), if it receives a systemic blood supply. Preoperative angiography is recommended as a valuable guide in planning surgery and delineating abnormal vessels, thereby lessening the possibility of hemorrhagic complications due to inadvertent damage during surgery (6–8). But none of these is used in the diagnostic investigation of a neonate with esophageal atresia and tracheo-esophageal fistula.

Communication between the esophagus or stomach and the accessory bronchopulmonary tissue causes complications resulting in death or chronic lung disease. Early diagnosis is essential if surgical treatment is to be curative. Should one lung fail to be inflated during thoracotomy and repair of tracheoesophageal fistula, the possibility that the lung may have an anomalous bronchial origin from the foregut must be considered. Attempts to correct the supposedly malplaced endotracheal tube and to inflate the lung will be unsuccessful and may result in extubation and subsequent disaster. This anomaly should also be suspected if the condition of a patient with esophageal atresia and tracheo-esophageal fistula does not entirely correlate with the diagnosis. A patient with a hazy lung on chest x-ray, cyanosis, or abnormal blood gases *at birth* should be investigated to rule out bronchopulmonary foregut malformation. Had the esophageal atresia and tracheo-esophageal fistula been successfully repaired without treatment of the bronchopulmonary foregut malformation, the latter condition would have resulted in severe morbidity, if not death, for the infant in the postoperative period.

Acknowledgments

The authors gratefully acknowledge the expert assistance of Mennen Alsol, M.D., resident in pathology, City Hospital Center at Elmhurst, New York, and The Mount Sinai Hospital, New York, NY.

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Submitted for publication February 1983.

The Mount Sinai Journal of Medicine
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Pancreatic Secretion: I. Effects of Vasopressin and Glucagon on Pancreatic Blood Flow and Secretion

Miklós Papp, M.D., Sc.D., Bertalan Varga, M.D., Gábor Varga, and Gábor Folly

In a previous report, it was shown that vasopressin decreased pancreatic blood flow (1) and prolonged the survival of dogs with experimentally induced acute pancreatitis (2–4). These favorable therapeutic results were thought to be the effect of preserving pancreatic blood flow in acute pancreatitis by maintaining cardiac output (5). Dreiling et al (6) found that the intravenous injection of 1 mg glucagon superimposed on continuous intravenous secretin infusion with 1 U/kg/hr decreased both pancreatic blood flow and secretion of dogs weighing 12–18 kg.

The aim of this investigation was (a) to determine pancreatic blood flow and secretion of dogs following administration of vasopressin, and (b) to study the hemodynamic effect of glucagon by which pancreatic blood flow and secretion might be affected. In a previous study, glucagon (1–8 μg/kg) injected into the superior pancreaticoduodenal artery was found to increase pancreatic blood flow without influencing the rate of pancreatic juice (7).

Material and Methods. Six male dogs (18.5 ± 0.8 kg) anesthetized by chloralose-urethane were used. After laparotomy, blood flow in the superior pancreaticoduodenal artery was measured by an electromagnetic flow meter. Blood flow was expressed as ml/min. Each dog received secretin (1 U/kg) infused into the femoral vein for 150 min. Vasopressin was infused in 0.1 U/kg into the contralateral femoral vein for 30 min. Pancreatic secretion was measured for flow and analysed for protein (8). The results were evaluated by analysis of variance using Dunnett contrasts (9).

Four male dogs (19 ± 2 kg) anesthetized by chloralose-urethane were used. After laparotomy, pancreatic blood flow was measured by heated thermocouples introduced into the tail and the head of the pancreas (7). Pancreatic tissue blood flow was registered by Hensel flugraph and arterial blood pressure was continuously monitored by Statham transducer in the femoral artery. An intravenous infusion of 8 μg/kg of glucagon was given for 10 min superimposed on a continuous intravenous infusion of 1 U/kg of secretin. Results were evaluated after analysis of variance using Dunnett contrasts (9).

Results. Vasopressin reduced pancreatic blood flow and pancreatic protein secretion decreased parallel with blood flow reduction (Fig. 1). After stopping vasopressin infusion, however, both pancreatic blood flow and secretion returned to control values.

Fig. 2 shows that glucagon administered with secretin background decreased pancreatic blood flow. Glucagon and secretin also decreased arterial blood pressure (Fig. 3).

Discussion. This is the first demonstration that the decrease in pancreatic blood flow induced by vasopressin reduced pancreatic secretion. When infusion of vasopressin was stopped, pancreatic secretion increased parallel with rising blood flow. These findings contraindicate the use of vasopressin in acute pancreatitis since ischemia, per se, may initiate pancreatic inflammation (10).

The glucagon data explain the previous failure of low-dosage glucagon administered into the pancreatic circulation directly to affect pancreatic secretion. When glucagon was given in higher doses together with secretin into the systemic blood circulation, it decreased arterial blood pressure and in this way, it reduced pancreatic blood

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Presented by Miklos Papp, M.D., November 1982, as a lecture during Visiting Professorship at the Department of Surgery, The Mount Sinai School of Medicine, CUNY, N.Y.

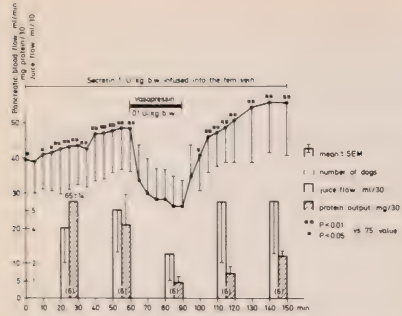

FIG. 1. Effect of vasopressin on pancreatic blood flow and protein secretion of dogs.

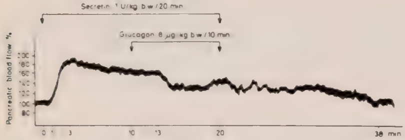

FIG. 2. Effect of glucagon combined with secretin infusion on canine pancreatic blood flow.

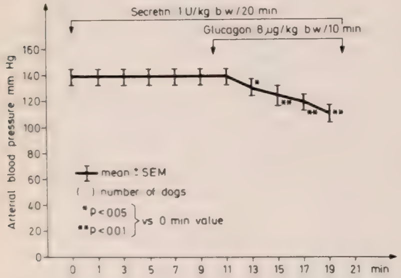

FIG. 3. Effect of glucagon combined with secretin infusion on arterial blood pressure of dogs.

flow and secretion. Low-dosage glucagon does not affect the systemic arterial blood pressure.

Summary. Vasopressin (0.1 U/kg) infused into the systemic blood circulation of dogs superimposed on secretin background (1 U/kg) reduced pancreatic blood flow and protein output parallel fashion.

Glucagon (8 μg/kg) infused into the systemic blood circulation of dogs superimposed on secretin background (1 U/kg) reduced arterial blood pressure and, in this way, pancreatic blood flow.

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Submitted for publication April 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Pancreatic Secretion: II. Pancreatic Duct Ligation and Protein Secretion in Cerulein-Stimulated Pancreatic Juice of Rats

MIKLÓS PAPP, M.D. SC.D., GÁBOR VARGA, AND GÁBOR FOLLY

In a previous report, pancreatic duct ligation for three hours was shown to decrease protein levels in secretin-CCK-stimulated pancreatic juice of rats after the release of ductal obstruction (1). This study confirms the previous data and indicates that a 3-hr ligation of pancreatic duct in rats decreases protein output in cerulein-stimulated pancreatic juice after the release of ductal ligation.

Method. Ninety CFY male rats (280 ± 10 g) were anesthetized by urethane and were subjected to laparotomy. The common bile duct was ligated at the hepatic hilum and the duct was cannulated close to the duodenum. The ninety rats were divided into 5 groups, each consisting of 18 rats. In Group 1, each rat received a bolus of 62.5 ng/kg of cerulein; in Group 2, 125 ng; in Group 3, 250 ng; in Group 4, 500 ng; in Group 5, 1000 ng/kg injected into the femoral vein. In each group, pancreatic juice was collected from 9 rats for 180 min, then the same dose of cerulein was given. After the second stimulus, juice was collected again for 60 min. The other 9 rats in each group were stimulated by the same dose of cerulein but the outflow of juice was obstructed for 180 min. Then the occlusion of the duct was released and the rats received the same dose of cerulein as a second stimulus given into the femoral vein. Finally the juice was collected for 60 min.

Juice samples were weighed and the protein levels were measured by the method of Weichselbaum (2). The results were evaluated after analysis of variance using Dunnett contrasts (3) and Student t-test; mean ± SEM was calculated.

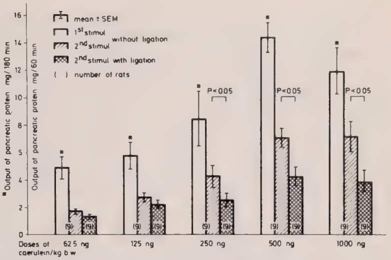

FIG. 1. Pancreatic protein output induced by graded and increasing doses of cerulein (62.5 ng-1000 ng/kg) given into the femoral vein of rats with or without 3-hr ductal ligation.

Results. Fig. 1 shows the protein outputs in pancreatic juice stimulated by graded and repeated doses of cerulein without and with ductal occlusion. The first dose of cerulein significantly increased the protein output of the pancreatic juice of intact rats. In the same rats, the second stimulus resulted in a lesser increase of protein output in the juice. The 3-hr occlusion, moreover, resulted in a significant and greater decrease in pancreatic protein secretion in all doses ranging from 250–1000 ng/kg of cerulein (Fig. 1).

Summary. The data indicate pancreatic ductal occlusion induces changes in the function of the acinar parenchyma which render it less sensitive to stimulation. These changes are in effect a defense mechanism which probably is active in pancreatic inflammations.

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Submitted for publication April 1983.

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Presented by Miklós Papp, M.D., November 1982, as a lecture during Visiting Professorship at the Department of Surgery, The Mount Sinai School of Medicine, CUNY, N.Y.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Pancreatic Secretion: III. Plasma Proteins and Pancreatic Secretion in Rats

MIKLÓS PAPP, M.D. SC.D., AND GÁBOR VARGA

In a previous communication it was shown that pancreatic secretory proteins administered intravenously to dogs and rats increased the protein level and output in the pancreatic juice of recipient animals (1). This is a report investigating whether the plasma proteins of donor rats injected into the bloodstream of recipient rats influence the protein level and output of pancreatic juice.

Twenty CFY recipient rats anesthetized by urethane were subjected to laparotomy. The common bile ducts were ligated at the hepatic hilum and were cannulated close to the duodenum to collect pancreatic juice for 60 min. Each rat received 1U/kg of secretin (GIH Lab.) given as a bolus into the femoral vein. Ten rats (310 ± 10 g) received fresh rat plasma (1 ml/kg = 56 mg protein/kg). Ten rats served as control (300 ± 8 g). Pancreatic juice samples of the recipient rats were weighed and protein level in the juice (2) was measured. The results were expressed as mean ± SEM and were evaluated statistically by using Student paired *t* test.

Fig. 1 (upper half) shows that plasma proteins injected into the circulation of recipient rats had no effect on the flow of pancreatic juice, protein level, or juice output compared to control values. For comparison, the lower half of Fig. 1 demonstrates the effect of pancreatic secretory proteins on the flow of pancreatic juice, protein level, and output. There was no difference in the quantity of injected proteins (56 mg/kg plasma protein vs 48 mg/kg pancreatic secretory protein).

Control groups		Treated groups	
(10) control		(10) blood plasma 0.1 ml/100 g b.w.	
Flow ml/60 min	0.10 ± 0.01•	0.09 ± 0.01	N.S.
Protein g/l	11.60 ± 2.88	11.10 ± 1.66	N.S.
Protein mg/60 min	1.05 ± 0.22	1.06 ± 0.23	N.S.
(10) control		(10) pancreatic juice 0.1 ml/100 g b.w.	
Flow ml/60 min	0.07 ± 0.01	0.08 ± 0.01	N.S.
Protein g/l	14.59 ± 1.32	20.03 ± 0.02	P<0.05
Protein mg/60 min	1.01 ± 0.12	1.54 ± 0.18	P<0.05

• mean ± SEM
( ) number of rats
N.S. non significant

FIG. 1. Effect of intravenously injected fresh rat plasma (upper half) and fresh rat pancreatic juice (lower half) on pancreatic protein secretion in recipient rats.

Summary. Plasma proteins injected into the circulation of recipient rats in dosage similar to pancreatic secretory proteins did not influence secretion of pancreatic juice, protein level, or juice output.

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Submitted for publication April 1983.

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THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Ophthalmologic Notes

Keith M. Zinn, M.D., Editor

Ocular Effects in Acquired Immune Deficiency Syndrome

JOEL S. SCHUMAN, B.A., AND ALAN H. FRIEDMAN, M.D.

The acquired immune deficiency syndrome (AIDS) was first described by the Centers for Disease Control in 1981 (1) and since that time over 1,000 cases of opportunistic infection, with or without Kaposi's sarcoma, have been reported (2). AIDS affects healthy young persons, especially male homosexuals (3–15), intravenous drug abusers (15, 16), hemophiliacs (17–23), and Haitians (24, 25). In addition, persons not in any of these groups have had symptoms characteristic of AIDS (26).

The etiology of AIDS is postulated to be a transmissible agent borne by blood or bodily secretion. The incubation period of the disease ranges from 9 to 22 months (2). Patients with AIDS manifest a prodrome characterized by weight loss, diarrhea, fever, and lymphadenopathy (3, 4, 10, 13, 27).

About one third of AIDS patients develop a virulent and aggressive form of Kaposi's sarcoma (KS); nearly one half develop *Pneumocystis carinii* pneumonia (PCP). About 7% have both KS and PCP. Twelve percent contract infections by one or more opportunistic agents. These infections include (a) pneumonia, meningitis, and encephalitis due to *Aspergillus, Candida, Cryptococcus,* cytomegalovirus, *Nocardia, Toxoplasma,* zygomycosis, or atypical mycobacteria; (b) progressive multifocal leukocephalopathy; (c) chronic enterocolitis due to cryptosporidiosis; and (d) extensive mucocutaneous *Herpes simplex* virus infection. Lymphomas have been reported in AIDS patients. There is a very high case fatality rate (greater than 40% to date) from this syndrome (3, 7, 14, 20, 27–29).

During the past two and one-half years, over sixty patients with AIDS were referred to us for ophthalmological examination. Many of these patients were seen in in-patient consultations. Of this group, 33 patients displayed retinal lesions associated with a number of the opportunistic agents known to afflict AIDS patients: lesions of cytomegalovirus in 18, *Pneumocystis carinii* pneumonia in 11, toxoplasmosis in 2, and fungal retinitis in 2. The salient clinical features for each of these four groups are summarized in the Table.

Cytomegalovirus Lesions. The retinal involvement in cytomegalovirus (31–34) produces such a distinct clinical picture that on several occasions the ocular diagnosis preceded virus isolation from various body fluids such as urine (Figure 1). The retinal lesions are white and granular ("crumbled cheese") and are nearly always associated with hemorrhage. These lesions progress so slowly that they may only double or triple in size in a month. As areas of retinal necrosis in one area of the retina resolve, large zones of atrophy become evident. Atrophic areas of retina were accompanied by pigment dispersion, vascular sheathing, and often by optic atrophy. Optic neuritis was seen on several occasions. As the focus of retinal necrosis enlarged, vitreous involvement increased and was observed as a cellular infiltration. Cytomegalovirus (CMV) was isolated from the vitreous ante mortem in one patient and was demonstrated in the retina post mortem in several eyes using immunoperoxidase techniques. The retinitis of CMV was totally unresponsive to all antiviral therapy, including acyclovir with or without interferon.

Postmortem histopathologic examination of eyes revealed extensive areas of retinal and retinal pigment epithelial necrosis. Typical intra-

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This work was supported in part by an unrestricted grant from Fight for Sight, Inc., New York, NY.

TABLE

Ocular Findings in Acquired Immune Deficiency Syndrome

Clinical Characteristics	Cytomegalovirus retinitis (N = 18)	*Pneumocystis carinii* pneumonia (N = 11)	Toxoplasmosis (N = 2)	Fungal retinitis (N = 2) *Candida albicans,* 1 *Cryptococcus sp,* 1
AIDS-Susceptible group				
Homosexual	16/18	8/11	1/2	0/2
Intravenous drug user	2/18	2/11	0/2	2/2
Hemophiliac	0/18	1/11	1/2	0/2
Median Age	28.2 years	27.8 years	20.5 years	23.4 years
Sex				
Male	18/18	10/11	2/2	2/2
Female	0/18	1/11	0/2	0/2
Race				
Black	12	3	0	0
White	2	8	2	0
Hispanic	4	0	0	2
Retinitis or Retinochoroiditis	18/18 (all bilateral)	not present	2/2 (unilateral)	2/2 (unilateral)
Vitritis	12/18	not present	2/2	2/2
Optic neuritis	7/18	not present	not present	not present
Anterior uveitis	3/18	not present	not present	not present
Cotton-wool spots	not present	11/11 (bilateral in 8)	not present	not present
Response to treatment	nil	resolved spontaneously	1/2	2/2
PCP	14/18	11/11	2/2	1/2
KS	3/18	2/11	0/2	0/2
Final outcome	14/18 died	—	1/2 died	1/2 died

nuclear and intracytoplasmic inclusions were seen. Electron microscopic studies confirmed the presence of virus and immunoperoxidase stains for CMV were positive.

***Pneumocystis carinii* Pneumonia.** The cotton-wool spots seen in patients with *Pneumocystis carinii* pneumonia are similar to those seen in diseases associated with the presence of circulating immune complexes or microvascular occlusive disease (Figure 2). (Circulating immune complexes have been observed in patients with *Pneumocystis carinii* pneumonia.) The cotton-wool spots are nearly always unassociated with hemorrhage. They lie in the superficial retina in the posterior pole and are usually an off-white color with an irregular border. Lesions are distributed helter-skelter. Cotton-wool spots tend to resolve in 6–8 weeks. As old lesions resolve, new ones appear. Postmortem histopathologic studies of eyes demonstrated typical superficial retinal cy-

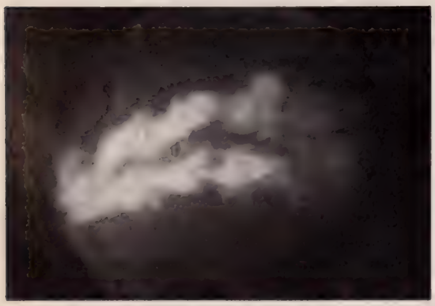

FIG. 1. Typical retinal lesion of cytomegalovirus, left eye. Involvement is paravascular. Retina contains large, irregular white area, "crumbled cheese" in texture, with associated hemorrhage. Optic nerve is encompassed by infectious process.

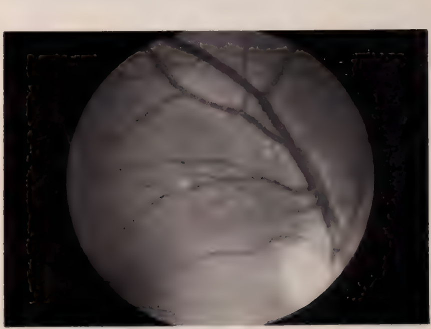

FIG. 2. Typical cotton-wool spots in fundus of right eye of patient with *Pneumocystis carinii* pneumonia.

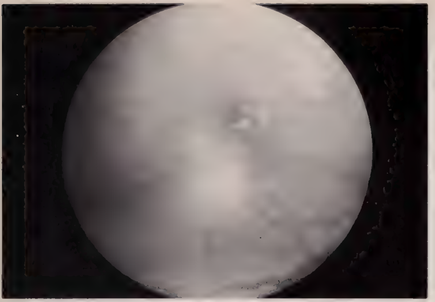

FIG. 3. Clinical photograph, toxoplasmosis retinochoroiditis; overlying vitreous haze.

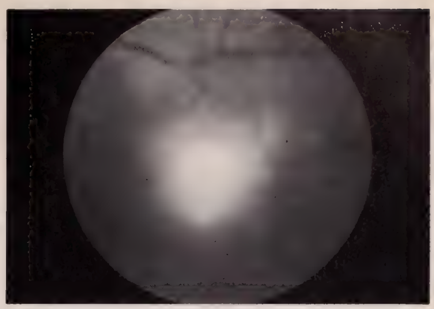

FIG. 4. Marked posterior pole involvement with *Candida albicans*. Numerous satellite lesions; initial focus has enlarged somewhat since first appearance; moderate overlying vitreous involvement.

toid bodies. No microorganisms were observed after special stains, nor were any seen in electron micrographs.

Toxoplasmosis. Clinically, toxoplasmosis is often manifest initially by floaters and blurred vision. Vitreous opacities and a white-yellow, slightly raised intraretinal lesion with irregular borders is seen (Fig. 3). There is little or no anterior uveitis. Resolution leaves a pigmented, often irregular, scar. Significant permanent loss of vision may develop if the lesion is located in the macula, papillomacular bundle, or optic nerve head. Lesions may encompass branch retinal arteries and produce a branch retinal artery occlusion. Juxtapapillary retinal lesions can mimic optic neuritis.

In the usual case of toxoplasmosis retinochoroiditis, as the vitreous clears, vision returns to normal so long as a vital area is not involved. There may be recurrent attacks, accompanied by photophobia, pain, redness, vitreous floaters, and decreased vision. Ophthalmoscopy reveals focal, necrotizing retinochoroiditis, often with perivasculitis (30).

In one of the two cases of toxoplasmosis, an old, healed, pigmented lesion was seen adjacent to the infectious focus but in the other case no other retinal lesion was noted. Postmortem histopathologic study of the latter eye revealed numerous *Toxoplasma* cysts within a necrotic retina.

Fungal Retinitis. The retinal lesions of *Candida* and *Cryptococcus* were quite like those we have previously observed in immunosuppressed patients (Figure 4). Fungal endophthalmitis characteristically produces small white-yellow retinal infiltrates. As the intraretinal focus of infection enlarges, the process spreads to the overlying vitreous and vitreous haze may be significant. The retinal lesions usually have fluffy borders and may range in size from less than one to several millimeters in size. Untreated, the lesions increase in size, produce vitreous abscesses, and lead to retinal detachment (30). As time progressed, our patients developed satellite retinal lesions. Vitreous involvement was a late feature. One patient survived his bout of cryptococcal retinitis after treatment with a variety of antifungal agents. Postmortem microscopic studies of the eyes of the other patient showed multiple microabscesses in all retinal layers. Special stains revealed many organisms.

Summary. The opportunistic infections associated with AIDS may occur in the eye as well as elsewhere in the body. The descriptions above should alert physicians dealing with AIDS patients to the ocular manifestations of the disease. The ophthalmoscopic examination of the AIDS patient often reveals a characteristic clinical picture that can assist the clinician in making diagnoses. Patients with the acquired immune deficiency syndrome should be routinely examined for ophthalmologic complications.

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Submitted for publication June 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Student's Corner

Barry Berson, B. A., Editor

Multiple Ulcerated Carcinoids of the Small Intestine with Hemorrhage: Report of Two Cases

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Abstract

Two unusual cases of multiple carcinoid tumors of the small bowel with ulceration and massive bleeding are described. Pertinent facts regarding carcinoid tumors are discussed and other previously reported cases are cited.

Carcinoid tumors of the small intestine are infrequent lesions usually discovered incidentally or diagnosed following the appearance of the well-known carcinoid syndrome. Occasionally they are diagnosed solely as a consequence of symptoms caused by local involvement of the small intestine. The following cases demonstrate the combined occurrence of two unusual presentations of a small-intestinal carcinoid tumor: severe gastrointestinal hemorrhage, and ulceration concurrent with multiple tumors. Carcinoid tumor not presenting as the carcinoid syndrome still poses a diagnostic problem to physicians even though, at times, there is massive involvement of the bowel wall. The importance of recognizing the unusual presentations of this tumor must therefore be emphasized.

Case Reports

Case 1. A forty-eight-year-old white man was admitted to The Mount Sinai Medical Center with a three-day history of maroon-colored stools and periods of dizziness. This was the fourth occurrence of such bleeding for this patient. The first episode had taken place two years previously, at which time he underwent extensive but nondiagnostic medical work-up. During the two subsequent episodes over the next fourteen months, the patient required replacement of large amounts of lost blood. At no time was a bleeding site located and all episodes resolved spontaneously. Previous work-up, including multiple colonoscopic and gastroscopic procedures, small and large bowel radiographic studies, and nuclear studies, were again nondiagnostic.

The patient had intermittent episodes of diarrhea for several years but no history of flushing, asthma, weight loss, or symptoms of heart disease. He had a known duodenal ulcer diagnosed 18 years prior to his admission and he had an appendectomy as a child. For one year prior to this admission he had taken cimetidine, 1.2 g/day. He had no history of excessive alcoholic consumption. The noteworthy physical findings on admission examination were a pulse of 84 beats per minute, supine, and 94 beats per minute, sitting, with a blood pressure of 134/78. The patient appeared to be well nourished and in no acute distress. The abdomen was flat, soft, and nontender. Bowel sounds were increased and no organs or masses were palpated. Black stool was present in the rectum and was guaiac positive.

Laboratory studies disclosed the following values: hemoglobin, 11.1 g/dl; hematocrit, 34.2%; total white blood cell count, 8.7 per cubic mm, showing no shifts in the differential count; prothrombin time, 10.4 seconds with control of 11.4 seconds. Routine chemistries were normal, with

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This paper was supported in part by the Serotonin Research Laboratory of the Mount Sinai School of Medicine.

a blood urea-nitrogen level of 20 mg%. X-ray studies of the abdomen showed a slightly dilated gas-filled colon. Contrast studies of the colon and small bowel were reported as normal.

The patient was admitted in stable condition, and the gastrointestinal bleeding ceased within the first twenty-four hours. Upper gastrointestinal endoscopy was performed on the patient's first day in the hospital and showed no lesion or signs of bleeding down to the third portion of the duodenum. Colonoscopy, however, revealed dark red blood in the caecum and ascending colon. No discrete bleeding site was demonstrated. It was therefore thought that the bleeding originated in the small intestine. The patient next underwent superior mesenteric angiography, which visualized a 3 cm, well-marginated, hypervascular lesion in the area of the terminal ileum (Fig. 1). To reproduce this finding, the procedure was repeated twice and, on the third injection of contrast, the patient was observed by the radiologist to have a paroxysmal episode of intense facial flushing lasting less than one minute. The possibility of a carcinoid tumor was at that point strongly considered. At laparotomy the following day, dozens of firm, submucosal tumors were found involving the small intestine from the distal jejunum to the mid-ileum (Fig. 2). They ranged from .5 cm to 1.5 cm in diameter. There was a stricture in the terminal ileum associated with one of the larger tumors and related to a cluster of nodes in the mesentery (Fig. 3). This lesion involved the serosal surface. Microscopic examination of the nodules revealed carcinoid tumor. Many of the nodules extended into the muscularis propria and were found to invade the serosa and mesenteric fat. The mucosa overlying most of these nodules was ulcerated (Figs. 4, 5). Three of the 22 mesenteric lymph nodes which were examined contained metastatic carcinoid tumor. A 5 ft portion of the small bowel was resected. The liver and the rest of the abdomen were examined and no other tumor nodules were discovered. The patient tolerated anesthesia and surgery well: An uneventful postoperative course followed. After surgery, a twenty-four-hour urine specimen disclosed normal values for 5-hydroxyindoleacetic acid (5 HIAA) and tryptamine. However, serum serotonin levels were slightly but definitely increased (0.35 μg/ml; normal, 0.09–0.31 μg/ml) and plasma tryptophan was slightly but significantly decreased (8.9 μg/ml; normal, 9.5–16.0 μg/ml) (1). An epinephrine provocation test failed to elicit a flush or hypotension. Liver and spleen scan was normal. The patient was discharged from the hospital to be followed with chemotherapy on an ambulatory basis.

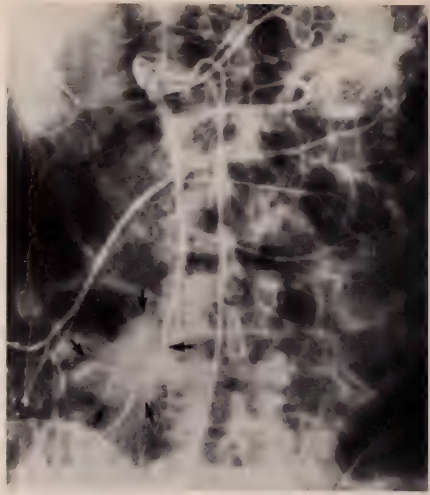

FIG. 1. Superior mesenteric arteriogram. Lobulated blush (arrows) supplied by the ileocolic branch; corresponds to lymph nodes containing metastatic carcinoid found at surgery.

Case 2. A 63-year-old white woman was admitted to a local hospital, where she was evaluated for mild respiratory distress and anemia secondary to gastrointestinal bleeding. During a ten-day stay she had consistent maroon-colored stools and at least one episode of hematemesis. Her hemoglobin dropped from 11.0 g/dl to 8.4 g/dl and she required 10 units of blood to stabilize 12 g/dl. She had peptic ulcer disease, for which surgery of unknown type was performed 20 years prior to this admission, and also had chronic obstructive pulmonary disease with bronchiectasis, and had undergone cholecystectomy and appendectomy. Barium enema revealed a huge polypoid lesion in the rectosigmoid, and upper gastrointestinal series showed evidence of prior vagotomy and Billroth II subtotal gastrectomy. Gastroscopy performed under general anesthesia confirmed the presence of this surgery and also revealed a long shallow erosion at the site of anastamosis. This lesion was friable but had no spontaneous bleeding. At colonoscopy, visualization was possible only to 30 cm because of copious jet black stool. The examination was considered unsatisfactory. The patient was then transferred to The Mount Sinai Medical Center for technetium 99

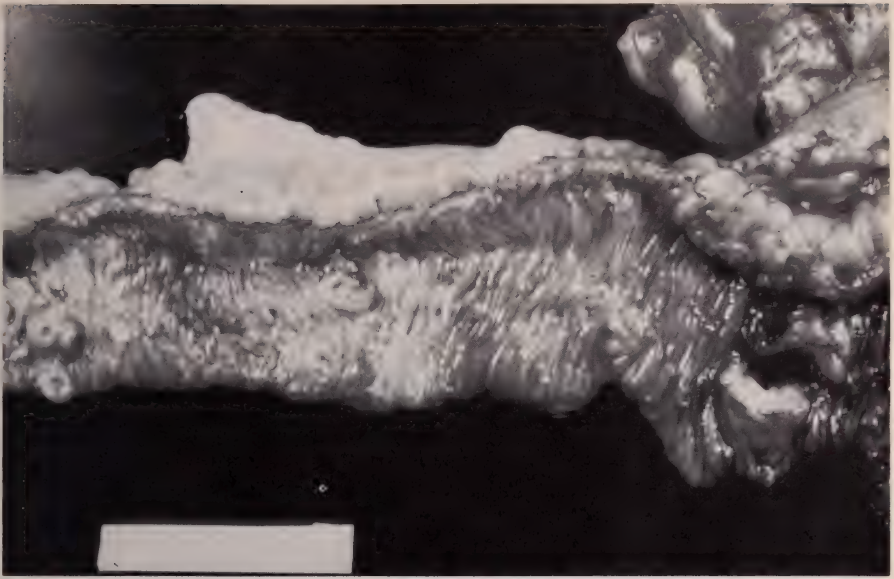

FIG. 2. Portion of ileum removed at surgery reveals multiple carcinoid tumors projecting into lumen with typical umbilicated appearance.

scanning. On admission her general appearance was of a pale, cachetic, white woman with marked facial hair in no acute distress. There were scattered ronchi on both lungs and she was coughing, with production of copious amounts of clear, white sputum. She had a 30-cm-long midline ventral hernia. Bowel sounds were normal and no masses or enlarged organs were palpated. The rectum contained black, guaiac-positive stool. No masses were felt.

Laboratory findings included hemoglobin, 12 g/dl, and hematocrit, 37%. Routine chemistries were normal. Technetium 99 scanning did not reveal a bleeding site.

Colonoscopy revealed a 4.5-cm multilobulated soft polyp at 20 cm with multiple satellite nodules (one-half removed), a 2-cm-diameter sessile polyp at 30 cm in the distal descending colon, and a 1-cm pedunculated polyp at 70–90 cm which was removed in fragments. Advancement of the colonoscope was stopped at 120 cm in the hernial sac because visualization of the lumen was obscured at this point by dark blood. Microscopic study of the sigmoid lesion revealed villous adenoma containing areas of in situ adenocarcinoma. At laparotomy on the seventh day of hospitalization, a left hemicolectomy was performed, and the ventral hernia repaired. Seven submucosal tumor nodules ranging in size from 0.5 to 1.2 cm were found in the terminal ileum with ulcerations of the overlying mucosa. The tumors were removed by multiple wedge resections. It was thought that the melena originated from this area. Microscopic examination revealed these small intestinal lesions to be carcinoid tumors invading the entire bowel wall with mucosal ulceration. The patient tolerated the surgery and anesthesia well and had an uncomplicated postoperative course.

No evidence of functioning carcinoid tumor was found. A 24-hour urine collection for indole metabolites revealed normal values for 5-HIAA, indoleacetic acid, and tryptamine. Blood serotonin and plasma tryptophan levels were within normal limits. At the time of this writing the patient is convalescing without complications. Other endocrine studies are scheduled to evaluate her marked hirsutism as a possible manifestation of multiple endocrine adenomatoses.

Discussion

Carcinoid tumor of the small intestine arises from the Kulchitsky (enterochromaffin) cell,

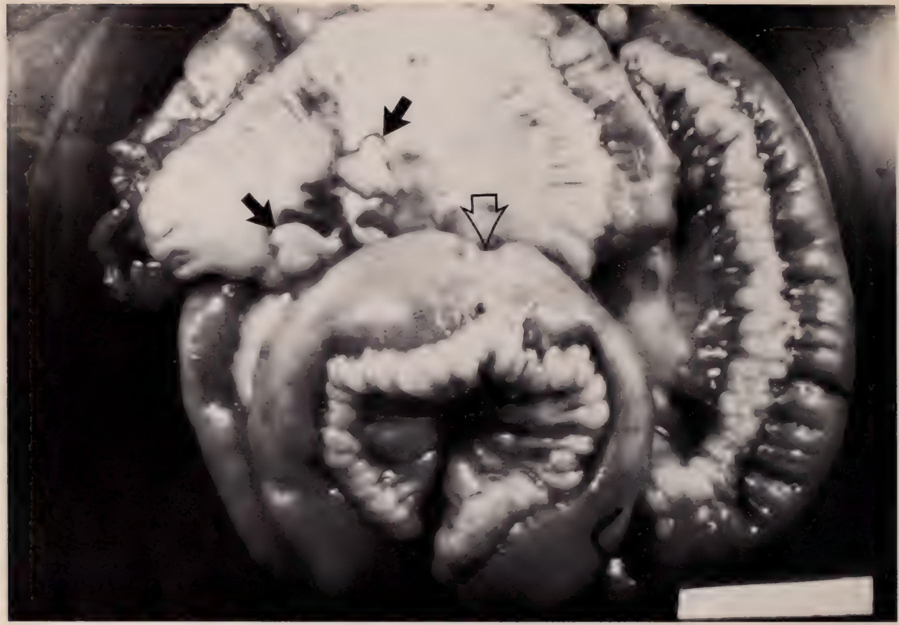

FIG. 3. Segment of resected small intestine with carcinoid tumor causing stricture of bowel wall (open arrow) associated with nodes in mesentery (black arrows).

making it a part of the APUD system (2). After the appendix, the small bowel is the second most common site of carcinoid tumor, but it is the most frequent site of malignant carcinoids. Although the incidence of carcinoid tumors of the small intestine accounts for less than 3% of all gastrointestinal tumors, the importance of recognizing its many presentations is stressed. The well-known carcinoid syndrome is usually seen only in cases where metastases have already occurred to the liver. However, in the absence of full-blown carcinoid syndrome, the tumor is infrequently diagnosed clinically. It is sometimes seen as an incidental finding at autopsy. Symptoms produced by carcinoid tumors which have not yet metastasized are attributable to local disruption of the bowel

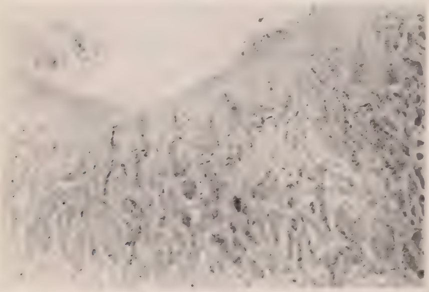

FIG. 4. Wall of small intestine with ulceration of mucosa (top) and infiltration of wall by nests of tumor cells (hematoxylin & eosin stain, ×40).

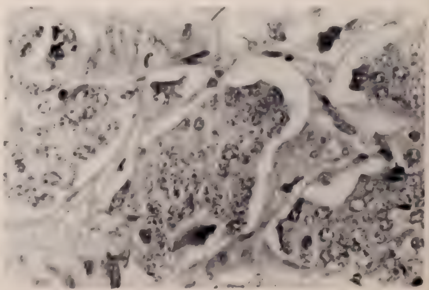

FIG. 5. Nests of polygonal tumor cells with round nuclei, fine chromatin, and granular cytoplasm (H & E stain, ×400).

wall. In a 1964 series by Moertel et al (3) of 209 patients with carcinoid tumors of the small intestine, 27% had symptoms attributable to local tumor invasion. Of these, abdominal pain was the major complaint, along with signs and symptoms of intermittent abdominal obstruction. Gastrointestinal bleeding was relatively uncommon and was subacute and chronic, without massive bleeding episodes. In a more recent (1982) series by Zeitels et al (4) of 101 patients, 39% were symptomatic. These authors report an incidence of gastrointestinal bleeding of 9%, only two lesions being in the ileum. In no case was the bleeding massive. However, sporadic cases of massive bleeding have been reported in the literature. Mann and Simpson (5) reported a 56-year-old man who had seven episodes of tarry stools over a 5-year period which had been repeatedly investigated without finding a source. In this case, only one carcinoid tumor site had been found in the distal ileum, which was determined to be ulcerated. Schwartz (6) presented a 52-year-old woman hospitalized 11 times for gastrointestinal bleeding. She was found to have a single 1-cm carcinoid tumor in the proximal ileum which had ulcerated. Other cases have been cited, including Gurnett and Hartigan (7) and Loebel et al (8). In all these unusual causes of gastrointestinal bleeding, none was due to ulceration of multiple carcinoid primaries, but rather to a single ulcerated lesion, even in cases where multiple primaries were found. The carcinoid tumor is a lesion which is submucosal. Extension of the tumor usually involves the muscularis propria and eventually the serosa and beyond. Rarely do these tumors ulcerate and, consequently, they bleed infrequently. The occurrence of simultaneous ulceration in multiple carcinoid tumors with superimposed bleeding is indeed unusual.

Multiple tumors have been reported to occur with a reasonably constant incidence. Moertel et al (3) report 29% incidence of a second carcinoid tumor when the first was found in the small intestine. This figure is consistent with the findings of other investigators: 28% by Pagtalunan (9), 33% by Ostermiller (10), 21% by Strauch (11). The only exception is the finding by Godwin (12), in a series of 2,837 cases of carcinoid tumors, of very few cases of multicentric carcinoids. Carcinoid tumor is considered multicentric if more than one tumor site is found. What is most frequently observed in such cases are multiple tumors of two or three primaries. Sometimes dozens of tumor sites are found, as in our cases. Shorb and McCune (13) described another case in which 96 separate carcinoid tumors were found in the small intestine. Other cases have been cited, but there have been no reported cases involving multiplicity with a significant number of primaries being ulcerated and bleeding.

Conclusions

The cases presented in this report clearly represent another of a wide variety of clinical manifestations of carcinoid tumor. Rarely does the physician have the opportunity of arriving at an accurate diagnosis when challenged by this uncommon tumor. Therefore, the recognition of these and other infrequent presentations of the carcinoid tumor must be emphasized. In cases where persistent gastrointestinal bleeding eludes diagnosis, the carcinoid tumor should be seriously considered.

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Submitted for publication July 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 5, September–October, 1983
Printed in U.S.A.

Student's Corner

Barry Berson, B.A., Editor

Pyoderma Gangrenosum in Crohn's Disease

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Abstract

Pyoderma gangrenosum is a rare, extraintestinal complication of Crohn's disease. The association between these two disease entities was explored in an effort to characterize their relationship. Anatomic extent of Crohn's disease, location of pyoderma gangrenosum, age of onset of both entities, and various treatments were considered.

Extraintestinal manifestations in inflammatory bowel disease have been subdivided into three groups. They appear to be of different etiologies, pathogenesis, and prognosis. Group A includes cases with skin, joint, eye, and mouth manifestations that are colitis-related. Group B cases evidence small-bowel pathophysiology with malabsorption, renal stones, gallstones, or noncalculous hydronephrosis. Group C applies to a third group of patients with nonspecific complications, including osteoporosis, liver disease, peptic ulceration, and amyloidosis (1).

Pyoderma gangrenosum is one of two main skin manifestations of Crohn's disease and is considered a rare extraintestinal complication of Crohn's disease (2). The association of pyoderma gangrenosum and regional enteritis was first described by Van Patter et al in 1954 (3). However, the relationship between the two disease processes is relatively obscure because neither disease is thoroughly understood.

In pyoderma gangrenosum the lesion may appear on any area of the body, including the mucous membranes. The lesions may be multiple or single and characteristically develop rapidly, beginning as a red plaque or pustule and spreading concentrically with necrosis and ulceration in the central portion of the lesion. A typical lesion has a necrotic ulcer, with an elevated overhanging border, immediately surrounded by a violaceous area which fades to erythema distally. The ulceration may enlarge quite rapidly in a few days (4). Histologic findings in pyoderma gangrenosum are nonspecific, and include necrosis, epidermal ulceration, edema, and infiltration by polymorphonuclear leukocytes and lymphocytes. Fibrinoid necrosis and vasculitis are usually absent (4).

Crohn's disease is often regarded as a homogeneous entity. Its clinical features, complications, and prognosis have been based on groups of patients studied rather than on classification of cases by anatomic site of involvement. However, anatomic involvement in Crohn's disease may directly determine the clinical course and prognosis of the disease itself as well as the associated complications (5).

Pyoderma gangrenosum, on the other hand, still remains a clinical enigma fifty years after its original description by Brunsting, Goeckerman, and O'Leary (6). Despite extensive study, its etiology remains uncertain and its pathology nonspecific (5).

Approximately half of all patients with pyoderma gangrenosum harbor underlying inflammatory bowel disease (7). Though most commonly reported with ulcerative colitis, pyoderma gangrenosum has been described in association with numerous other conditions. These include inflammatory diseases (Crohn's disease; proctitis; duodenal, gastric, or oral ulcers; polyarthritis; rheumatoid arthritis; and inflammatory pulmonary disease), metabolic disease (iron deficiency, diabetes mellitus), neoplastic disease (chronic my-

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This paper was written when the first author was a fourth-year student at Mount Sinai School of Medicine. Address reprint requests to Department of Surgery, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York NY 10029.

TABLE

Clinical Characteristics, Pyoderma Gangrenosum (PG)

Pt. No.	Sex	Crohn's site*	Age at onset Crohn's/PG	PG site	Treatment	Response† PG/Crohn's	Indication for surgery	Surgical procedure	Response† PG/Crohn's	PG symptoms follow Crohn's activity	Other group A Manifest.
1	F	RE	19/19	legs, trunk, vagina	prednisone Azulfidine	1/2 3/2	NA	NA		yes	mouth joint
2	M	RE	42/48	legs	prednisone	1/2	Crohn's	ileocolic resection	1/2	yes	skin, nonspecific dermatitis
3	F	GC	32/41	legs, buttocks	IV steroids prednisone Azulfidine	1/1 2/2 3/2	Crohn's	subtotal colectomy	1/2	no	joint
4	M	GC	42/42	legs	IV steroids prednisone Azulfidine Immuran	1/1 2/2 2/2 3/3	NA	NA		yes	none
5	F	GC	6/11	legs	prednisone Azulfidine	3/2 3/3	Crohn's	subtotal colectomy	2/2	no	joint mouth
6	M	GIC	26/32	legs	prednisone Azulfidine	2/1 3/3	Crohn's	subtotal colectomy	2/2	yes	eye *E. nodosum*
7	F	GIC	48/54	legs	prednisone Azulfidine ACTH	2/2 2/2 ?/2	Crohn's	total proctocolectomy, ileal resection × 2	2/2	yes	eye joint
8	M	GIC	4/15	legs	prednisone Azulfidine Immuran	2/2 2/2 2/2	Crohn's & PG	total proctocolectomy	1/2	yes	joint *E. nodosum*
9	F	GIC	16/27	legs	prednisone Azulfidine ACTH Immuran	2/2 2/2 2/2 1/1	NA	NA		yes & no	mouth
10	M	GIC	21/21	legs, face, underarm	prednisone Azulfidine Immuran	2/2 2/1 3/3	Crohn's	subtotal colectomy	2/1	no	joint eye
11	M	GIC	17/20	legs	prednisone Azulfidine	?/2 ?/2	Crohn's	?	?/?	?	none
12	F	GIC	14/25	pubic region	prednisone Azulfidine ACTH	?/? ?/? ?/?	Crohn's	colectomy proctocolectomy	?/?	yes	none
13	F	GIC	19/27	legs	prednisone ACTH	?/? ?/?	NA	NA		?	mouth joint *E. nodosum*
14	F	GIC	41/43	upper extremities	prednisone Azulfidine	1/1 3/3	NA	NA		?	eye joint

* RE = regional enteritis, GC = granulomatous colitis, GIC = granulomatous ileocolitis, NA = not applicable.

† 1 = responded well, 2 = responded then relapsed, 3 = no response, ? = unknown.

Other results: no patients had any prior known immunodeficiency.

elogenous leukemia, acute myelogenous leukemia, lymphoblastic leukemia, polycythemia vera, multiple myeloma, and Hodgkins disease), and several immunodeficiency states (8, 9).

An immunologic etiology of pyoderma gangrenosum is currently favored. In recent years, considerable evidence of grossly altered immunity has been demonstrated in patients with pyoderma gangrenosum. Interestingly, the immune defects have varied greatly from patient to patient and no common defect has yet become apparent. Abnormalities of humoral immunity, cell-mediated immunity, and complement have all been described. Thus, the pathogenesis of these skin lesions appears to be heterogeneous (9, 10).

What makes the immunologic theory more appealing is the fact that group A extraintestinal manifestations of Crohn's disease may all have an immunological basis (1). Joint, skin, and eye involvement in Crohn's disease may be due to the deposition of antigen-antibody complexes in synovium, skin, and the choroid apparatus of the eye (1). Other theories supporting an immunological basis for this disease are proposed by Brunsting and his associates, who state that the cutaneous manifestations of pyoderma gangrenosum are "but one part of a generalized infectious syndrome characterized by a marked lowering of bodily resistance to invading organisms" (6). Another theory is that of Callen and Taylor (4), who believe that pyoderma gangrenosum is a primary or secondary hypersensitivity reaction. The two most prevalent hypotheses are (a) that the skin and colonic lesions are produced by the same etiologic agent, or (b) the skin reflects the primary disease of the bowel via an allergic angiitis or a Shwartzman phenomenon (4).

In the past, pyoderma gangrenosum has been observed most often in ulcerative colitis, whereas erythema nodosum is more frequently observed in granulomatous colitis (1). However, Shore believes that erythema nodosum may in fact be an early lesion of pyoderma gangrenosum (9). Shore goes on to say that many of the other lesions seen with pyoderma gangrenosum are in reality abortive forms of the same pathological process (9). This is significant when considering the absolute incidence of pyoderma gangrenosum in patients with Crohn's disease.

Most of the early publications on pyoderma gangrenosum were limited to reports of single cases. Other papers looked at skin manifestations associated with Crohn's disease rather than pyoderma gangrenosum specifically.

Methods

We have reviewed the charts of all patients admitted to The Mount Sinai Hospital between January 1, 1960 and May 31, 1981 with a discharge diagnosis of Crohn's disease. The number of patients with Crohn's disease totaled 1,010; 383 had regional enteritis, 455 had granulomatous ileocolitis, and 172 had granulomatous colitis. Fourteen patients with Crohn's disease also had been diagnosed as having pyoderma gangrenosum at one time or another during their illness.

The diagnosis and extent of Crohn's disease was based on clinical impression, radiographic study, and endoscopic examination. The diagnosis of Crohn's disease was confirmed by pathological examination of resected or biopsied bowel in each case.

The diagnosis of pyoderma gangrenosum was based on clinical criteria as described by Callen and Taylor (4). Neither specific pathological criteria nor unique laboratory changes have as yet been established as diagnostic of pyoderma gangrenosum. The clinical criteria included the appearance of a painful, rapidly enlarging ulcer beginning as an erythematous plaque, vesicle, or papule which developed into a destructive ulcer with necrosis and further ulceration in the central portion, the ulcer having an irregular border with ragged and purple-red overhanging edges and the whole area being surrounded by an erythematous areola (4).

Information was obtained by chart review supplemented with direct questioning of the patient. Four of the 14 patients found to have both disease entities had incomplete clinical records; the patients were lost to follow-up and could not be contacted. Some data on these 4 patients were included in the charts and in our numerical calculations when appropriate.

Results

Pyoderma gangrenosum occurred in 1.4% of the patients with Crohn's disease. Of the 14 patients, 2 (14%) had Crohn's involvement limited to the small intestine. In 3 (21%), disease was limited to the colon, and the remaining 9 patients (65%) had Crohn's disease involving both the large and small bowel. Eight females and 6 males were included in this study.

The age at onset of Crohn's disease ranged from 4 to 48 years (average, 25). The average age at onset of pyoderma gangrenosum was 30, the range being from 11 to 54 years of age.

Twelve of 14 patients had pyoderma gangrenosum of the lower extremities. Other areas of skin involvement included the chest, upper extremities, pubic area, buttocks, and face.

The severity of the skin lesion was found to be mild in half of our patients, and severe, to the point of incapacitation, in the other half. Preceding trauma was not implicated as the cause of the skin lesion in any of the patients.

We were able to obtain information regarding the relationship of the pyoderma gangrenosum to the course of their underlying bowel disorder in 11 patients. A definite association was reported by 7 patients; 1 patient reported an association in one episode but not in another; 3 patients reported no relationship.

Eleven of 14 patients were found to have other group A extraintestinal manifestations.

Discussion

Rankin et al of the National Cooperative Crohn's Disease Study on Extraintestinal Manifestations found that among 569 patients with Crohn's disease, 24% had a history of at least one extraintestinal manifestation. Twenty-six (4.6%)

had either pyoderma gangrenosum or erythema nodosum. Looking at the anatomic classification, it was noted that 5 of these patients (19.2%) had granulomatous colitis, and 6 (23.2%) had regional enteritis while the majority, 15 patients (57.6%), had granulomatous ileocolitis (7). In a similar study by Greenstein et al of 498 patients with Crohn's disease, 69 (13.9%) had skin manifestations; 14 of these (20.3%) had granulomatous colitis, 36 (52.2%) had granulomatous ileocolitis, and 19 (27.5%) had regional enteritis (1).

These two studies looked at both erythema nodosum and pyoderma gangrenosum. If indeed these two skin manifestations are different stages of the same process, as Shore believes, we may be grossly underestimating the incidence of pyoderma gangrenosum in our study. Our reported incidence of pyoderma gangrenosum in patients with Crohn's disease is similar to the findings of Farmer et al (5). In 615 patients with Crohn's disease they found 9 patients (1.5%) who had both pyoderma gangrenosum and Crohn's disease. Fifty-six percent had Crohn's disease limited to the colon, as opposed to 21% in our study. Forty-four percent had ileocolic involvement as compared to 65% in our study. They reported having no patients with regional enteritis having pyoderma gangrenosum while we had two patients with both pyoderma gangrenosum and regional enteritis. All of this data is in agreement with previously published findings that pyoderma gangrenosum occurs more frequently in patients with Crohn's disease with colonic involvement (4, 5).

The male-to-female ratio (3:4) in our study is somewhat different than the 2:3 ratio found by Perry in an earlier study of patients with pyoderma gangrenosum (2). The sex ratio of patients with Crohn's disease is roughly equal (11).

Using the average age at onset of disease, we found that bowel disease preceded the onset of skin disease by five years.

The average age at onset of Crohn's disease in our study is compatible with the 15- to 35-year-old range for age at onset reported in the literature (11). The average age at onset of pyoderma gangrenosum in our study is compatible with that reported by Perry (2). There have been cases in which the ulcers of pyoderma gangrenosum have preceded the onset of abdominal symptoms (2); therefore, appropriate evaluation of a patient with pyoderma gangrenosum should include a search for underlying inflammatory bowel disorders. In spite of an exhaustive search, Perry reports that at least 15% to 20% of cases of pyoderma gangrenosum are idiopathic (2).

The location of the pyoderma gangrenosum in our patients is compatible with results reported by McGarity and Barnett (12), Shore (9), and Korelitz and Sommers (13).

Trauma was not implicated as the cause of the skin lesion in our patients, consistent with an earlier study by Perry who found trauma to be a precipitating factor of pyoderma gangrenosum in patients without gastrointestinal disease (2). Since the pathogenesis of pyoderma gangrenosum is unknown, there is no effective specific therapy. Current treatment includes symptomatic relief and nonspecific medications that appear to work clinically (4, 13). Perry suggested that the use of cleansing tubs and wet dressings with pHisoHex or potassium permanganate was useful local care (2). Other agents more commonly recommended are Azulfidine, sulfonamides, sulfones, and corticosteroids. Recent attempts at treating pyoderma gangrenosum have included the use of immunosuppressives, Dapsone, and intralesional steroids. Successes as well as failures are reported for each of these modalities (4, 13, 14). Clofazimine, perhaps the newest agent to be used, is known to improve phagocytic activity of neutrophilic leukocytes. Its efficacy lends some support to the immunological theory of pyoderma gangrenosum (10). Clofazimine appears to be of some benefit, but it is not a panacea (10).

Perhaps the most widely accepted approach to the treatment of pyoderma gangrenosum is that attention must be paid to the general health of the patient, especially in relation to the control of bowel pathology (15). Evidence supporting this approach is that Bishopric and Bracken described dramatic improvement of the skin lesion following resection of the involved segment of intestine (8). Results of an unpublished study by Talansky et al suggest that prompt skin healing may occur following definitive surgery in patients with severe inflammatory bowel disease, but not necessarily in those with milder forms of disease (16).

Our results indicate that no treatment is clearly and consistently effective. Many agents have been tried, and although some have provided relief over a period of time, none have done so regularly. The factors which influence the course of pyoderma are still poorly understood. Until more is known about the etiology and pathogenesis of this rare complication of inflammatory bowel disease, it is unlikely that a reliable form of therapy will be found to be effective in all cases.

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Submitted for publication August 1982.

The Mount Sinai Journal of Medicine
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Pharmacologic Control of Gastric Acid Secretion in Peptic Ulcer

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Peptic ulcer disease is thought to occur because of relative or absolute gastric acid hypersecretion. Although the etiology of peptic ulceration remains unknown, a considerable number of pathophysiologic abnormalities have been proposed to explain how gastric acid hypersecretion contributes as "aggressive" factor to the formation of gastroduodenal ulceration.

Pathophysiologic Abnormalities

In 1952, Cox (1) reported that the number of parietal cells in the stomach of duodenal ulcer (DU) patients was approximately twofold greater than in healthy subjects. The overlap between the DU patients and the normal subjects was large; about two-thirds of ulcer patients fell within the normal range. It was not established whether the parietal cell number was genetically determined, but it has recently been reported that hyperpepsinogenemia I, which reflects the number of peptic cells in the stomach and closely correlates with maximal acid outputs, is inherited as a single autosomal dominant gene (2).

DU patients as a group tend to release greater amounts of gastrin in response to protein meal than normal subjects (3). Since gastrin exhibits a trophic effect on gastric mucosa (4, 5), it is possible that the genetic predisposition in DU patients results from greater postprandial release of gastrin, which in turn causes the increase in the number of parietal cells.

The increased gastric acid secretory capacity, which is based upon the increased number or "mass" of parietal cells, occurs only in some of those DU patients who secrete more than normal individuals (6). The proportion of patients with abnormally high gastric secretory capacity who do not develop duodenal ulceration has, however, not been defined—nor have the factors which determine whether a gastric hypersecretor or a normosecretor will develop an ulcer. What is certain is that the maximal acid secretory response to stimulants is determined not only by the parietal-cell mass and the G-cell mass but also by other factors, including the functional state of the secreting cells and the presence or absence of gastric mucosal diseases, particularly gastritis. Baron (7) observed that DU patients have a greater "drive" to secrete acid than normal subjects. This is reflected in two- or three-fold greater basal acid secretion in DU patients compared to normal subjects (8). The explanation for the difference is still unknown. Feldman et al (8) claimed that it reflects increased vagal activity because some of their DU patients with high basal acid secretion failed to augment this secretion in response to physiological vagal excitation such as sham-feeding. Other possible mechanisms of increased basal secretion in DU may include increased sensitivity to gastric secretagogues or simply the increased parietal cell mass.

Some studies have emphasized the increased sensitivity of DU patients to secretory stimulation. Isenberg et al (9) found that DU patients required significantly lower doses of exogenous pentagastrin to produce one-half maximal gastric acid output, and that the dose-response curve for acid secretion to pentagastrin was shifted to the left. More recently, Lam et al (10) reported that DU patients secreted relatively more acid than healthy controls in response to endogenous gastrin released by liver extract meals.

Walsh et al (11) demonstrated that DU patients exhibited decreased inhibition of acid secretion and gastrin release after intragastric instillation of acidified amino acid meal. This was confirmed by Lam et al (12), who observed that gastric acid secretion in DU patients in response to amino

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acid plus cornstarch meal was relatively less suppressed at meal pH 2.5 than in normal subjects. This indicates that DU patients have a defect in the inhibition of gastric acid secretion and gastrin release at intragastric acid pH as compared with nonulcer subjects.

Several studies measured the duodenal pH and observed that duodenal bulbar pH tended to be lower in DU than in normal subjects under both basal and postprandial conditions (13). This has been explained by more rapid gastric emptying and increased duodenal acid loads, as indicated by earlier studies of Hurst (14) and Shay (15) and confirmed more recently by Malagelada et al (16). There may be an impairment of the inhibition of gastric emptying by acid in duodenum of DU patients (17), but other factors—such as defective release of secretin or other duodenal inhibitors and the deficiency of duodenal disposal of acid—may also contribute to the apparent lower duodenal pH in DU patients.

There is, however, no direct evidence that any of these pathophysiological abnormalities and secretory defects have a specific role in the pathogenesis of peptic ulceration. Hence, the shift of emphasis from studies of "aggressive" factors toward more careful examination of defense mechanisms (18). It has been correctly pointed out that while a substantial number of individuals show gastric acid-pepsin hypersecretion, only a few develop peptic ulcerations. Thus, peptic ulcer may occur because of too little mucosal resistance rather than too much acid-pepsin secretion. Among the protective mechanisms, attention has been directed to the possible importance of mucus secretion, the gastric mucosal barrier, the mucosal cells, the mucosal circulation, and the mucosal generation of prostaglandins (19).

Goals of Medical Therapy

The goals of medical therapy of peptic ulcer include the control of episodic ulcer "activity" with characteristic pain pattern, and the prevention of recurrences and complications, thereby influencing the natural course of the disease. A number of drugs have been developed and used to treat peptic ulcer disease. Although some drugs, such as carbenoxolone (20) and prostaglandins (21), have been said to improve mucosal resistance and to accelerate the healing of peptic ulcer, the mainstay of ulcer therapy still remains reduction in gastric acidity, with emphasis on anticholinergics, tricyclic agents, histamine H_2-receptor antagonists, methyl prostaglandins, and—most recently—inhibitors of proton "pump."

Inhibition of Secretion by Isolated Parietal Cell

In vitro studies of canine or human isolated parietal cells have demonstrated that these cells have specific receptors for each of the three classical stimulants, acetylcholine, histamine, and gastrin, and that antagonists of these receptors act in a predictable, specific fashion (22). Histamine appears to be the only secretagogue capable of stimulating and maintaining secretory activity via activation of the adenylate cyclase-cyclic AMP system (23); cholinergic agents and possibly gastrin appear to be regulatory devices to determine the magnitude of the histamine response (Fig. 1). Surprisingly, gastrin as a single stimulant produces only a small increase in secretory activity through an unknown mechanism, and anticholinergics or H_2-blockers have little influence on this effect. Cholinergic stimulants act via activations of specific muscarinic receptors and enhancement of Ca^{++} influx into the parietal cells, effects that can be blocked by specific antimuscarinic agents or calcium removed from cell surroundings (24). Since histamine and acetylcholine seem to be constantly released in the mucosa by most cells (histamine) and cholinergic nerves (acetylcholine), they provide a paracrine or neurocrine background stimulation for the parietal cells that greatly potentiates the action of gastrin on these cells (Fig. 2). The interaction between histamine and gastrin or histamine and cholinergic stimulation seems to occur beyond the parietal cell receptors. It may be of great importance in modulating parietal cell response under physiological conditions such as feeding, when the release of gastrin shows phasic increase and the potentiating interaction between this hormone and histamine or acetylcholine background can occur (25).

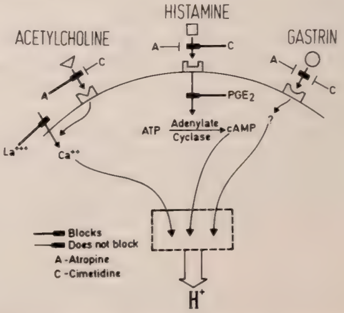


FIG. 1. Parietal cell receptors; effects of activation and blockade (22).

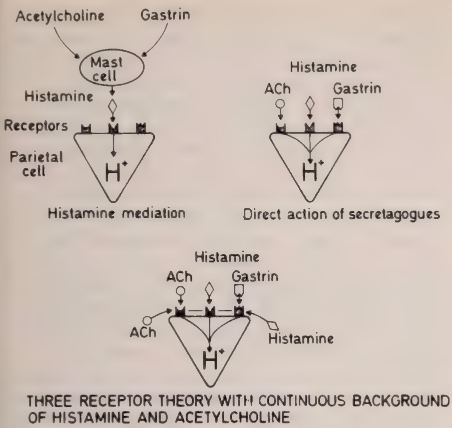


FIG. 2. Three concepts of activation of parietal cell to secrete acid (25).

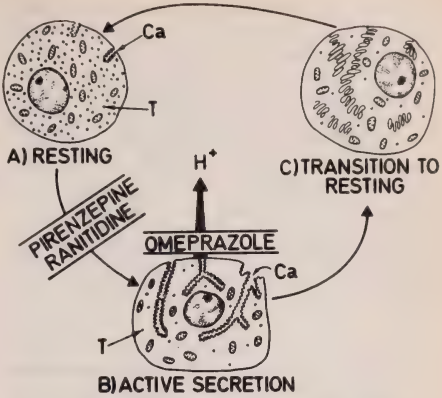


FIG. 3. Morphologic transformation of parietal cells upon stimulation without and with blockade by antisecretory agents. Resting cells (A) are characterized by numerous cytoplasmic tubovesicles (T) and a few secretory cannaliculi (Ca) with microvilli. During active secretion (B), tubovesicles (T) are depleted at the expense of a great increase in size of secretory cannaliculi. After acid secretion has ceased (C), cannaliculi collapse, lose microvilli, and are thought to reform the numerous tubovesicles of the resting cell. Ranitidine or pirenzepine prevents change from resting to active state; omeprazole does not prevent morphologic transformation but blocks secretion of acid (27, 32).

In the in vitro parietal cell preparation, blockade of cholinergic receptors by antimuscarinic agents abolishes the stimulatory effect of acetylcholine acting alone and removes the cholinergic component of potentiating interaction between this neuromediator and other stimulants. Similarly, the blockade of H_2-receptors by cimetidine abolishes the effect of histamine acting alone and removes the histaminic component of potentiating interaction between histamine and other stimulants (26). These findings suggest that in vivo, when parietal cells are exposed to constant background stimulation of histamine and acetylcholine, which sensitizes the cells to phasically released gastrin, anticholinergics withdraw the sensitizing action of background acetylcholine, while H_2-blockers remove the potentiating action of the background histamine stimulation.

The blockade of receptors by anticholinergics or H_2-blockers prevents the usual cyclic morphological transformation of parietal cells from resting to secreting state and also prevents recycling of membranes between tubovesicular system and cannalicular microvilli (27) (Fig. 3).

Prostaglandin E_2 (PGE_2) is a potent inhibitor of parietal cells but the mechanism of its action has not been explained. It appears to reduce the stimulation of the parietal cells exposed to histamine alone or to histamine in combination with gastrin or cholinergic agents, but not exposed to gastrin, cholinergic stimulant, or cyclic AMP alone or in combination. Thus PGE_2 seems to be a specific inhibitor of histamine stimulation and probably acts by suppression of histamine activation of the parietal cell adenylate cyclase (28).

The cellular mechanism of inhibition of parietal cells by benzimidazole derivatives such as omeprazole (29) is completely unrelated to the blockade of hormonal receptors or interference with second messengers mediating secretagogue action on these cells. Benzimidazole derivatives seem to inhibit the activity of H^+-K^+-ATP-ase, an enzyme unique to the gastric mucosa and located in the membrane of cannalicular secretory surface (30). They act on the final step in acid secretory processes, peripheral to the site of activation of cyclic AMP, and result in the inhibition of proton "pump" on the secretory cannalicular surface (31) (Fig. 4). This explains why benzimidazole derivatives do not affect the poststimulatory morphological transformation of parietal cells but block only the active transport of H^+ to the secretory cannaliculi (32).

Reduction in Gastric Acidity

Anticholinergics. Naturally occurring anticholinergics are tertiary amines (for example, atropine or L-hyoscyamine), which antagonize muscarinic receptors, while most of the synthetic agents are quaternary ammonium compounds,

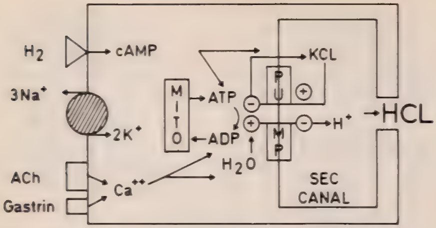


FIG. 4. Model of some aspects of parietal cell stimulation via muscarinic, histaminic, and gastrinic receptors, intracellular 2nd messengers, and proton pump at the cannalicular surface (30).

which also have some ganglion-blocking (nicotinic) activity (33). The anticholinergics are used to competitively inhibit the effects of acetylcholine, released from pre- and post-ganglionic cholinergic fibers, on the muscarinic receptors of parietal cells (22). Most of these drugs tend to suppress the secretory activity of all exocrine digestive glands, and it is questionable whether any of them exhibits selective action on gastric acid secretion (34). There is great individual variation in sensitivity to anticholinergics, and an "optimal effective dose" has been suggested for satisfactory inhibition of gastric secretion (35).

Anticholinergics inhibit basal and nocturnal secretion by about 40%–50% (36); vagal secretion by 50%–70% (37); and postprandial secretion by approximately 30%–40% (38) (Fig. 5). The secretory inhibition resulting from oral administration of long-acting anticholinergics was found to be somewhat less pronounced than that induced by surgical vagotomy (35, 38) (Fig. 6). Ivey (34), who reviewed the findings of reasonably well controlled secretory studies with orally applied conventional anticholinergics, reached the conclusion that the reduction of basal and histamine- or food-induced acid secretion was achieved at the maximal recommended doses or at doses several times higher, but not with recommended routine doses. Such high doses prompted several side effects, such as blurring of near vision, mydriasis and consecutive photophobia, alteration in the heart rate (tachycardia), difficulty with micturition, inhibition of gastrointestinal motility, and depressant effects on central nervous system. These weak gastric antisecretory properties and significant side effects of anticholinergics made them unsuitable as sole treatment for peptic ulcer therapy. The long-term effects of anticholinergics in peptic ulcer disease are controversial, though it has been claimed that maintenance treatment with these drugs resulted in reduction of recurrences and ulcer complications (39).

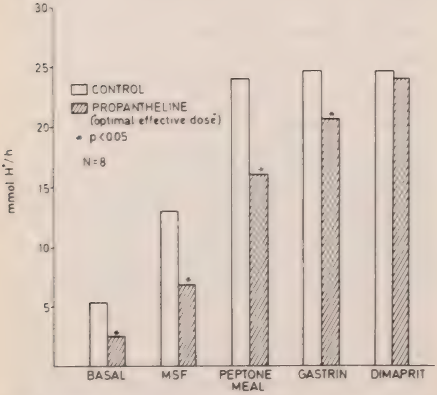


FIG. 5. Effect of propantheline given in "optimal effective dose" on gastric acid secretion, under basal conditions and following maximal stimulation by modified sham-feeding (MSF), gastric peptone (10%) meal, gastrin, and dimaprit in 8 duodenal ulcer patients.

Tricyclic Antidepressants and Related Drugs. This group includes tricyclic antidepressants such as pentobarbital, diazepam, or trimipramine as well as prienzepine. The rationale of the clinical use of these psychoactive agents is based on the assumption that "masked depression" plays some role in DU disease. The most encouraging effects were obtained with trimipramine, probably because its mild anticholinergic and H_2-blocking properties mildly reduce basal and pentagastrin-stimulated secretion (40). A few clinical trials with trimipramine (41, 42) indicate that the drug is effective in healing of gastric and duodenal ulcers, but unpleasant side effects similar

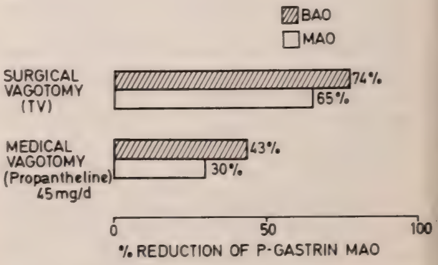


FIG. 6. Comparison of reduction in basal (BAO) and maximal (MAO) secretion induced by pentagastrin after pharmacological ("medical") vagotomy induced by oral treatment with propantheline (45 mg/d) and subsequent surgical truncal vagotomy in the same 10 duodenal ulcer patients.

to those observed after anticholinergic therapy were observed in a high percentage of patients, particularly in first days of treatment.

Pirenzepine is also a tricyclic compound structurally similar to psychotropic tricyclic drugs but devoid of any effects on the CNS because it virtually does not penetrate the blood-brain barrier (43) (Fig. 7).

Pirenzepine inhibits gastric secretion of acid and pepsin under basal conditions and following sham-feeding, food, insulin, pentagastrin, and histamine stimulation in healthy subjects and DU patients (37, 43–45). The degree of inhibition depends on the dose of the drug and the type of stimulation (Fig. 8). The most sensitive was basal and vagal stimulation, which was suppressed by about 50% when a side-effect-free or "optimal effective" dose of pirenzepine was administered (37). Several reports have suggested that the drug is more gastroselective than other anticholinergics and capable of inhibiting gastric secretion at a dose level without undesirable side-effects. These findings and in vitro binding studies (46) suggest the existence of subclasses of muscarinic receptors with high affinity (gastric acid secretion, gastrin release) and low affinity (salivary secretion, smooth muscle activity, heart rate) for pirenzepine (47). Pirenzepine, unlike other anticholinergics, does not raise the postprandial serum gastrin level in acute dosages and causes rather small elevation in serum gastrin during prolonged therapy.

Several clinical trials with pirenzepine performed recently in various countries showed that it was superior to placebo and similar in effectiveness to cimetidine for both healing and release rate, but some tolerable side effects were more common with pirenzepine (48). Several studies comparing pirenzepine and cimetidine (48) showed that they were usually effective in healing duodenal ulcer, but cimetidine had a slight advantage by producing greater symptomatic relief in the early stage of treatment (Fig. 9).

Histamine H_2-blockers. Histamine has a powerful stimulatory action on gastric acid secretion and may serve as the final common mediator for other secretagogues by activating histamine H_2-receptors of the parietal cells (49).

The blockade of H_2-receptors by a classical H_2-blocker such as cimetidine (Fig. 10) resulted in a dose-dependent and competitive inhibition of histamine-induced gastric secretion (50, 51). This drug also suppressed gastric secretion induced by other exogenous stimulants (pentagastrin, caffeine) (51, 52) or endogenous stimulants (sham-feeding, food, amino acid meal, gastric distension) (53, 54). In comparison with anticholinergics, H_2-blocker provided stronger inhibition (up to 90%) of basal, nocturnal, and postprandial secretion and had no influence on serum gastrin, mucosal blood flow, or functional integrity of gastric mucosa (53–56).

The effectiveness of cimetidine in the inhibition of all modes of gastric secretion suggests that histamine may serve as the final common mediator of acid secretion (mediator hypothesis) or that it sensitizes the oxyntic cells to other stimuli (permissive hypothesis) (Fig. 11).

After prolonged H_2-blocking therapy, maximal acid secretory capacity tended to decline, probably due to a transient decrease in the ability of the oxyntic cells to secrete acid but not because

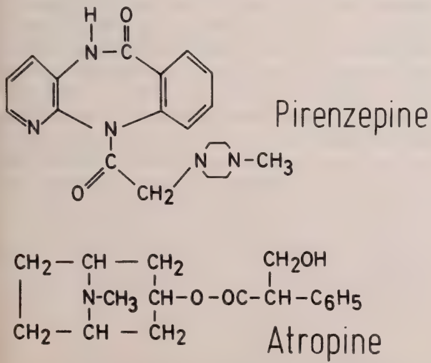


FIG. 7. Chemical structure of pirenzepine and atropine.

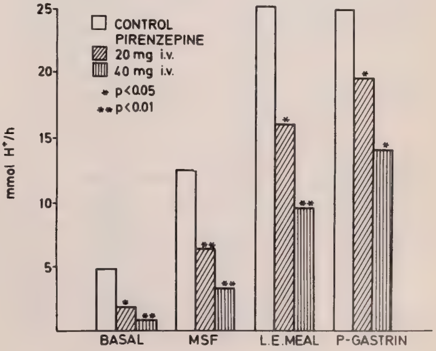


FIG. 8. Effects of pirenzepine, 20 or 40 mg IV, on gastric acid secretion under basal conditions and following modified sham-feeding (MSF), 5% liver extract meal, and pentagastrin in the same 6 duodenal ulcer patients.

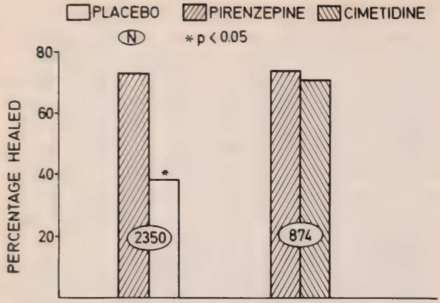
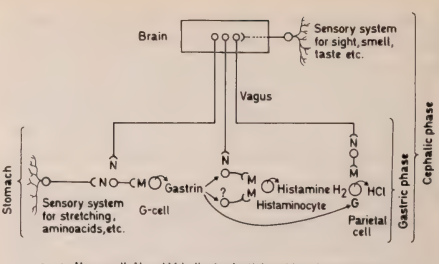


FIG. 9. Percent of complete endoscopic healing of duodenal ulcers treated for 4–6 weeks in double blind trials by pirenzepine vs. placebo and pirenzepine vs. cimetidine. Figures in circles indicate total numbers of subjects treated (48).


Brain
Sensory system
for sight, smell,
taste etc.
Vagus
Cephalic phase
Stomach
N
N
N
M
C N
C M
Gastrin
?
M
M
Histamine
H2
HCl
G
Sensory system
for stretching,
aminoacids, etc.
G-cell
Histaminocyte
Parietal
cell
Gastric phase

o—c = Nerve cell. N and M indicate nicotinic acid and muscarinic cholinergic transmission respectively.

FIG. 11. Gastric secretory mechanisms and role of histamine, gastrin, and cholinergic innervation in cephalic and gastric phase.

of reduction in parietal cell mass, as secretory status returned to normal soon after discontinuation of H_2 treatment (57, 58). With prolonged H_2-blocking therapy serum gastrin tends to increase, probably due to removal of the acid inhibition of gastrin release (55, 59).

A number of double-blind and placebo-controlled therapeutic trials with cimetidine revealed that the drug is superior to placebo in healing duodenal ulcer (60). The endoscopic healing rate after 4–6 week treatment reached 80%–90% with cimetidine or ranitidine as compared to 25%–40% with placebo. In comparison with intensive antacid or pirenzepine therapy, cimetidine yielded similar healing but with less side effects. Cimetidine may also be useful in the treatment of gastric ulcers and ulcers recurring after gastric surgery even if acid secretion is low (61). Prolonged cimetidine treatment may effectively control acid secretion and heal ulcerations in the Zollinger-Ellison syndrome but a few cimetidine-resistant cases have been reported (62).

Correlation of pretreatment acid secretion with ulcer healing by H_2-blockers showed that raised basal (BAO) and maximal (MAO) acid secretion have been found to hinder ulcer healing in some populations (63, 64). Also hypersecretion was associated with higher release rate in long-term prophylactic trials with cimetidine (65). Among patients on cimetidine maintenance treatment, recurrence rate was about 25% a year (65). The absolute amounts of acid secretion blocked was similar in those who relapsed and in those who continued in remission. However, because pretreatment MAO was greater in the relapsed group the proportion of secretion blocked was less than in those who maintained healing. Bianchi Porro et al (64) also observed that hypersecretors (MAO over 35 mmol H^+/h) on long-term maintenance treatment with 0.4 g cimetidine nocte relapsed at higher rate than normosecretors. Since the degree of gastric inhibition was related to the concentration of H_2-blocker in the circulation, it has been suggested that in some patients the blood level of the drug may be insufficient because gastric secretory capacity is much greater than normal. Indeed, increasing the dosage of cimetidine with increase in the drug blood level sometimes resulted in the healing of duodenal ulcers "proved" to be resistant to normal dosage (64). In an attempt to augment and prolong gastric inhibitory effects of H_2-blockers, long-acting anticholinergics or pirenzepine have been administered with H_2-blockers. It has been claimed that

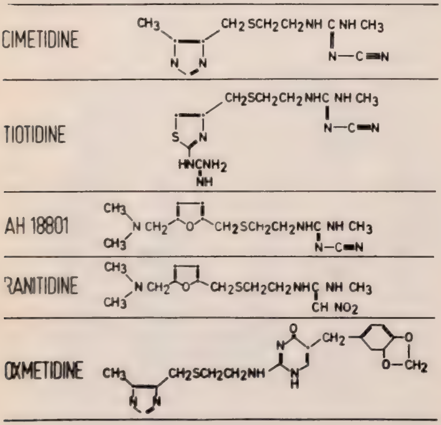

CIMETIDINE
CH3
CH2 SCH2 CH2 NH C NH CH3
N—C≡N
N
N
TIOTIDINE
CH2SCH2CH2NHC NH CH3
N—C≡N
S
N
HNCNH2
NH
AH 18801
CH3
N CH2
O
CH2SCH2CH2NHC NH CH3
CH3
N—C≡N
ANITIDINE
CH3
N CH2
O
CH2SCH2CH2NHC NH CH3
CH3
CH NO2
XMETIDINE
CH3
CH2SCH2CH2NH
O
N
CH2
O
O—CH2
N
H
N
N

FIG. 10. Structure of cimetidine and novel H_2-receptor antagonists currently being tested in clinical trials in peptic ulcer therapy.

the combined therapy successfully increased the degree of gastric inhibition, compared with H_2-blockers alone (45, 46), but other reports have failed to demonstrate any such effects (67).

Although cimetidine has been remarkably "safe," several adverse reactions have been reported, including inhibition of liver drug metabolism, antiandrogenic action, stimulation of prolactin release, CNS effects (60). It appears that in addition to binding at H_2 receptors, cimetidine binds at other sites in the body, and these interactions lead to clinically important side effects in some patients. The best known additional binding sites are (a) cytochrome P450, which is part of the mixed oxygenase enzyme system in the liver which oxydizes and inactivates many important drugs including propranolol, diazepam and warfarin; inhibition of this enzyme system by cimetidine can markedly potentiate and prolong the action of drugs; (b) androgen receptors; the resultant antiandrogenic action occasionally causes gynecomastia and sexual dysfunction in the male; (c) an uncharacterized binding site in the CNS, whose occupation may lead to mental confusion, particularly in the elderly; (d) an uncharacterized binding site on peripheral blood lymphocytes which mediate their activation. Since some of these bindings were not linked with H_2-receptor blockade, attempts were made to synthesize new H_2-blockers devoid of these side-effects.

The new generation of H_2-blockers is still growing. At present the most promising seems to be ranitidine, which is not only completely free of side effects but also more potent and longer acting (67, 68) (Fig. 10). It differs from cimetidine in the structure of both its ring and substituent. Cimetidine and the earlier H_2-blockers described by Black et al (50) are imidazole derivates like histamine itself. Indeed, these workers considered imidazole moiety to be important for activity and they achieved the necessary H_2-receptor selectivity of action and potency by varying the substituents carried on the ring. Ranitidine has a general shape similar to cimetidine though its detailed chemistry is different; it is a derivate of furan but not of imidazole and its ring substituents are different from those of cimetidine. Single oral dose of ranitidine produced considerable gastric acid inhibition lasting about 12 hours; therefore, twice daily dosage of this drug was recommended for prolonged therapy (69) (Fig. 12). Ranitidine, 150–200 mg twice daily, suppressed more 24-hour gastric acidity than cimetidine, 1000 mg four times daily (70).

A number of recent clinical trials of short-term and maintenance treatment with ranitidine showed conclusively that this agent is superior to placebo and at least as effective in healing ulcer as cimetidine (71); because of the easier dosing regimen and absence of side effects, ranitidine was preferred (Fig. 13). Ranitidine was found highly effective in cimetidine-resistant duodenal ulcer and Zollinger-Ellison syndrome patients, probably due to better control of gastric acidity with ranitidine (62).

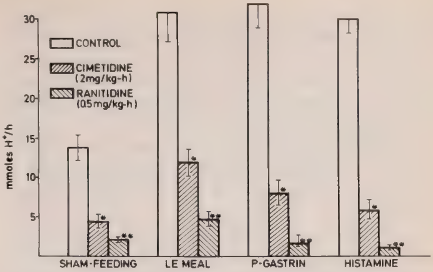


FIG. 12. Comparison of cimetidine and ranitidine in inhibition of gastric acid responses to modified sham-feeding (MSF), 5% liver extract meal, pentagastrin, and histamine in 8 duodenal ulcer patients (68).

Prostaglandins. Gastric mucosa generates substantial quantities of prostaglandins (PG) of E and I series, which have been considered to be feedback inhibitors of acid secretion, potent vasodilators, and protective agents (72).

Natural PGs are effective gastric inhibitors only after parenteral (not oral) administration because of their quick degradation in the gastrointestinal mucosa (73). In contrast, methylated PGE_2 analogs such as 15(R)-15methyl PGE_2 ($MRPGE_2$) or 16,16-dimethyl-PGE_2 ($DMPGE_2$) are extremely potent gastric acid inhibitors, par-

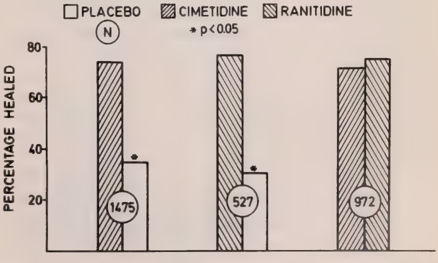


FIG. 13. Percentage of complete endoscopic healing after 4–6 weeks of treatment in double-blind trials with cimetidine vs placebo, ranitidine vs placebo, and cimetidine vs ranitidine. Numbers in circles indicate total number of duodenal ulcer patients in trials (71).

ticularly when given orally, owing to their local action on the oxyntic glands. They produce potent inhibition of basal, nocturnal, and meal-, pentagastrin- or histamine-induced gastric secretion for some hours after a single oral dose (72–76). They suppress the release of gastrin (74) and preserve mucosal integrity against various irritants (aspirin or ethanol) at doses much lower than required to inhibit acid secretion (72, 77) (Figs. 14, 15).

Only a few double-blind clinical trials with PGs have been performed. They have shown that PGs are superior to placebo in accelerating healing of duodenal ulcer. $MRPGE_2$, 200–400 μg/day given over 4 weeks, increased the healing rate from about 40% in placebo group to about 60%–90% in PG-treated groups (78–80). These effects could be attributed to inhibition of acid secretion as well as to gastric cytoprotection. The latter possibility is supported by the finding that natural PGE_2 given orally was capable of increasing the healing rate of gastric and duodenal ulcerations, although it had no effect on gastric secretory rate (21, 81). The major drawbacks of PG therapy are loose stools and diarrhea, which occur in a substantial proportion of treated patients. These effects result from the stimulation by PGs of intestinal secretion and motility (72).

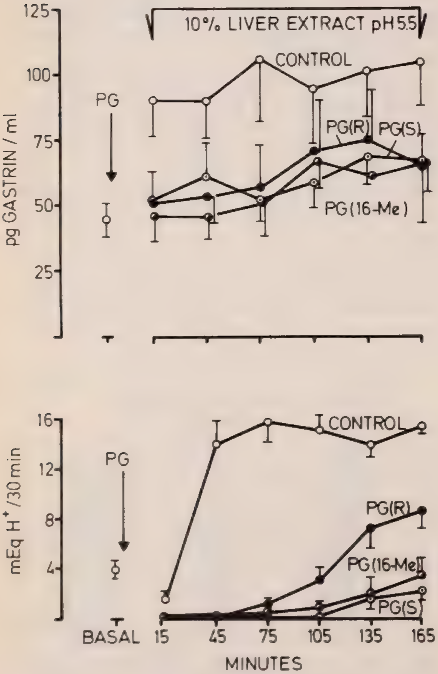


FIG. 14. Effects of the methyl PGE_2 analogs on serum gastrin and gastric acid responses to 10% liver extract meal in healthy subjects (75).

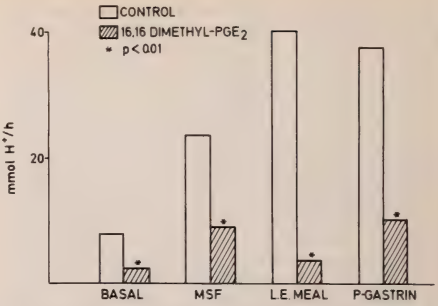


FIG. 15. Effects of 16,16,dimethyl PGE_2 (oral, 100 μg) on basal, modified sham-feeding, 5% liver extract meal, and pentagastrin-induced acid secretion in 8 duodenal ulcer patients.

Inhibitors of Proton Pump. Benzimidazole derivates such as omeprazole (Fig. 16) are potent antisecretory agents that specifically inhibit H^+ K^+-ATPase involved in the proton pump delivering H^+ at the cannalicular surface of the parietal cells (29, 31). Benzimidazole derivatives counteract the activity of these cells induced by all modes of stimulation of H^+ secretion. Unlike anticholinergics or H_2-blockers, benzimidazole derivates do not prevent the usual poststimulatory morphological transformation of the parietal cells from resting to active state, but only block H^+ secretion (32). Since H^+ K^+-ATP-ase is located solely in the parietal cells, benzimidazole derivates specifically inhibit only H^+ secretion, without affecting other parameters of the functional state of the stomach or other portions of the digestive system (31).

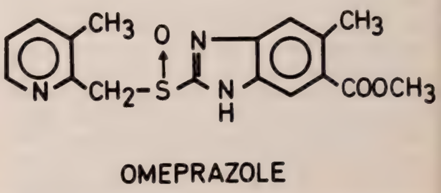


FIG. 16. Chemical structure of omeprazole, a representative benzimidazole derivative (29).

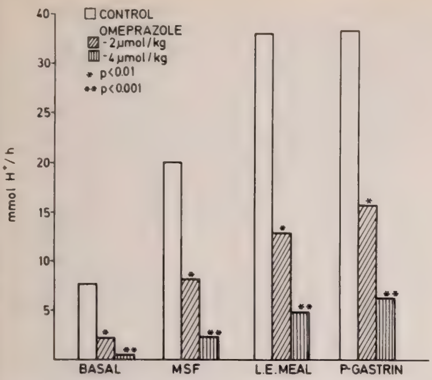


FIG. 17. Effects of omeprazole (oral, graded doses) on gastric acid secretion under basal conditions and in response to modified sham-feeding (MSF), 5% liver extract meal, or pentagastrin in the same 6 duodenal ulcer patients.

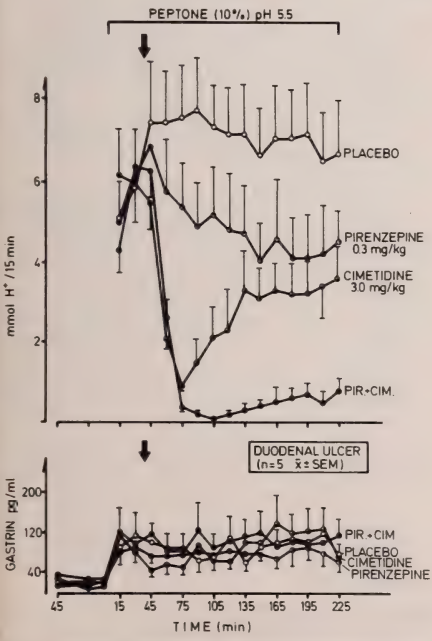


FIG. 18. Effects of pirenzepine and cimetidine given separately and in combination on gastric acid and serum gastrin responses to a peptone meal in 5 duodenal ulcer patients (45).

Omeprazole, a most potent representative of benzimidazole derivates in rather low dosage in humans, inhibits gastric H^+ secretion under basal condition and in response to sham-feeding, ordinary feeding, and pentagastrin (31) (Fig. 17). It does not influence basal or postprandial gastrin release and does not produce any side effects. Preliminary results of clinical trials in ulcer disease and Zollinger-Ellison syndrome now in progress indicate that these derivatives may soon become a mainstay of ulcer therapy.

Combinations. Several studies evaluated how combinations of antisecretory drugs can increase inhibitory action and reduce dosages (60). Most of these combinations include anticholinergics, which are mild inhibitors when given alone and are recommended as adjunctive therapy with H_2-blockers or antacids. A combination of anticholinergics with H_2-blockers (45, 82) or PGs (83) usually produced an additive inhibitory effect on meal-induced H^+ secretion (Fig. 18) but, curiously, did not reduce 24-hour gastric acidity below that obtained with H_2-blockers or PGs alone (84). Clinical evaluation of combined therapy in ulcer disease has not been reported except for a few patients with Zollinger-Ellison syndrome; in these, H_2-blocking therapy was rendered more effective by adding anticholinergics (86).

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Submitted for publication March 1983.

The Mount Sinai Journal of Medicine
Vol 50, No. 6, November–December, 1983
Printed in U S A

Environmental and Occupational Factors in General Medical Practice

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Abstract

Environmental and occupational factors are important causes for a broad spectrum of diseases. Cause-effect relationships between exposure and clinical findings are often obscure. For many occupational diseases, these relationships can be confounded by multiple exposures, either concurrent or sequential, and by clinical effects that are not pathognomonic. A long period of clinical latency (20–40 years) between onset of exposure and the clinical manifestation of the disease adds to the difficulty. It is therefore important to seek a detailed occupational history exploring exposures even of short duration over the patient's working lifetime. Further, it is advantageous to explore personal habits, such as hobbies, smoking, and alcohol consumption. Work experiences of family members may point to exposure to hazardous agents brought home on the worker's clothes, unknowingly. The physician may play a key role in the early detection and prevention of occupational and environmental diseases, many of which are major contemporary public health problems.

The impact of the environment on health has received increased attention during recent years, and environmental factors are now considered the cause for a broad spectrum of diseases (1). Occupational diseases constitute a significant portion of environmentally induced illnesses, many of which are well-defined pathological and clinical entities. But, because of the complexity of both the general and occupational environment, it is sometimes difficult to relate clinical symptoms and signs to one particular agent. Moreover, both patients and physicians are often unaware of a possible cause-effect relationship between exposure and clinical findings. Since occupational and environmental diseases may involve several organ systems, patients with such diseases may come to the attention of physicians of different specialties. Also, their evaluation often requires the participation of physicians from several medical disciplines.

In view of the rapid growth and technical development of modern industry, which requires the use of new chemical substances and technologies, it is anticipated that an increasing number of patients with effects of occupational and environmental exposures will come to the attention of the medical and scientific community.

This review describes characteristics of occupational and environmental diseases and discusses the importance of the occupational and general environment as disease-causing factors. Moreover, since occupational and environmental factors are responsible for a significant proportion of malignant diseases (2), and since therapeutic possibilities are limited, prevention is of utmost importance. This can be achieved by avoidance of exposure or, where exposure has already occurred, early diagnosis and treatment by appropriate medical intervention.

Recognition of Risk

One basic requirement for the successful diagnostic evaluation of a patient with occupational or environmental disease is the physician's awareness of a possible relationship between a particular clinical syndrome and exposure. In some instances, the risk is easily perceived; for example, in the case of acute poisoning the con-

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nection is often obvious; for instance, a farmer, spray pilot, or agricultural worker handling pesticides, such as the organophosphates (Parathion, Malathion), who presents with acute organophosphate poisoning with all its cholinergic manifestations, is often correctly diagnosed and managed (3). In other instances, as after exposure to the widely used isocyanates (toluene diisocyanate, TDI; and methylene diphenyl diisocyanate, MDI), the onset of an asthmatic reaction may occur only during the night following the exposure at the workplace. Similar delayed reactions have been reported in enzyme detergent sensitivity (4). Also, so-called "metal fume fever," characterized by myalgia, chills, temperature elevation, and leukocytosis, occurs a few hours after exposure to metal fumes of alloys, particularly those containing cadmium and zinc. The short time lapse between exposure and effect facilitates diagnosis and treatment. Etiologic factors can be identified by the physician who takes a medical history which includes a detailed review of events preceding the acute symptoms. For the diagnosis and therapeutic handling of toxicologic emergencies, the reader is referred to a recent text on that subject (5).

However, in many instances, clinical manifestations of occupational and environmental diseases occur several decades after the exposure (latency period), and we emphasize below some problems which a clinician may encounter in the evaluation of patients with such long-term effects.

Latency—"Silent Incubation Period." One important characteristic of certain occupational and environmental diseases—occupational cancer in particular—is the long period of clinical latency between first onset of exposure and clinical manifestations of the disease. This implies a "silent" period between exposure and the time when the disease becomes clinically observable. For mesothelioma, one of the asbestos-associated cancers, this latency is commonly 30–40 years (6). A similar lag between exposure and disease has been demonstrated for other chemicals as well. Exposure to some aniline dyes which contained β-naphthylamine and benzidine has induced bladder cancer in workers 20 years or more after exposure (7). The association between hepatic angiosarcoma and previous exposure to vinyl chloride was only recognized in the early 1970s (8); significant exposure began in the 1940s–1950s as part of the development of the plastics industry.

This chronological feature can also be applied to one of the most common cancers, lung cancer and its relationship to cigarette smoking. This disease was uncommon three or four decades ago. The increase now observed in the United States is related to the sharp rise in cigarette consumption that began in the 1930s. Because of changing smoking patterns in recent years, lung cancer is now also much more common in women (9), among whom smoking widened in the 1950s and 60s.

Two additional sources of exposure have a long latency period: radiation (10) and intake of DES (diethylstilbestrol) (11). Although radiation sickness is a well-known acute clinical entity, delayed neoplastic effects are still being observed among survivors of the Hiroshima-Nagasaki atomic bomb explosion (10). As for the effects of DES, the "latency period" pertains to the vaginal cancer reported in 17–20-year-old female offspring of mothers who used this medication during their pregnancy for threatened abortion. The effect of smoking and alcohol intake on the fetus, and subsequent development of neurological disease, should also be noted (12, 13).

The delay in recognizing cancer risk associated with previous occupational and environmental exposures is reflected nowadays in an increasing number of cases; for some diseases, the problem has become a worldwide public health issue. The rapid technical development of modern industry required the introduction of new chemical agents; and the biological effects of many currently being used have not yet been well-defined. It may be that large populations are now in the midst of a period of "clinical latency" from the effects of compounds of uncertain long-term neoplastic potential. For instance, carcinogenic risk has only recently been identified in workers exposed in the metal industry to cutting fluids containing nitrosamines (14), an observation that should raise the awareness of the medical community about an occupational risk which may manifest itself only after several decades.

Multiple Factor Interaction. The complexity of the work environment necessitates consideration of the interaction and perhaps the synergistic effects of industrial agents (15). The concept of "one cause, one effect" has been applied to many occupational diseases and has been the basis upon which threshold limit values and standards have been developed during the last decades. However, this approach has been narrow and unrealistic. The worker's job title may not really reflect the multiple exposures experienced, and "hidden" but pathogenetically important exposures may easily be overlooked by the physician. A "mechanic" in a machine shop can be exposed to metals and metallic compounds, but also to solvents and cutting oils. A brake maintenance worker may experience exposure to asbestos, mineral oils, and degreasing agents (frequently solvents). Other groups of workers with exposure to a multitude of compounds include painters, construction workers, foundry workers, coal miners, primary lead smelters, and those employed in chemical plants and refineries. Unfortunately, only limited information is available on the mechanisms of interaction among environmental agents.

This issue becomes even more complex when evaluating the effects of interaction between environmental agents and factors reflecting the worker's lifestyle, such as food habits, alcohol intake, and smoking. Additional factors which may operate in the workers' general environment outside the factory include physical factors such as heat (16), cold (17), and radiation. The association between exposure to ultraviolet light and skin and lip cancer has long been recognized (2).

An example of an enhanced cancer risk resulting from synergism is the interaction between asbestos and cigarette smoking (18). Pursuant to an initial observation in the mid-1930s that asbestos might be implicated in lung cancer (19), epidemiological investigations proved such a relationship, with an extraordinarily high mortality in lung cancer among asbestos-exposed individuals. Some investigations have shown that 20% of asbestos workers die of lung cancer (20). Although asbestos alone is implicated in the development of lung cancer, there is a strong synergistic effect with the addition of cigarette smoking. The recognition of this interaction is of great practical clinical importance in preventing lung cancer among asbestos-exposed individuals; at the present time, the cessation of cigarette smoking is the only known way to decrease the high risk of lung cancer development in these individuals. Once exposure has occurred, only cessation of smoking seems to diminish the risk; asbestos workers who stop smoking reduce their risk to about one-half or one-third of those who continue to smoke (20). It is evident that the physician's awareness of the hazardous asbestos-cigarette smoking interaction is a key factor in lowering this risk.

"Signal" Diseases. The effects of some compounds are quite specific with regard both to biochemical-metabolic effects and to the clinical pathological entities which ensue. Historically, initial demonstration of the relationship between occupation and disease—cancer in particular—has often been the result of observant clinicians who have added an epidemiological approach to their practice. Thus, when noticing a high incidence, within a relatively short time, of rare tumors in certain working populations, a cause-effect relationship can be suspected. Such observations, albeit on a limited scale, have often proven to be epidemiologically significant and correct. This applies, for example, to nasal and sinus carcinoma and their relationship to woodworking (21) and nickel compounds (22) respectively; similar observations have also established the association between hepatic angiosarcoma and exposure to vinyl chloride (23).

The potential association between lung cancer and asbestos exposure was first suspected in a single case report in 1935 (19), when bronchogenic carcinoma was still a rare tumor in the general population; since that time, of course, it has become very common, and represents about 15% of all cancer. On the other hand, pleural and peritoneal mesothelioma, which are specific asbestos-related tumors and common among both smoking and nonsmoking asbestos-exposed persons (24), have remained extremely rare tumors in the general population even today.

Experiences such as the foregoing demonstrate that individual physicians may be in the vanguard for the early detection of serious occupational and environmental diseases in the future.

Absence of Pathognomonic Syndromes. The recognition of a cause-effect relationship is sometimes difficult when the clinical effects are nonspecific. This applies particularly to effects on the central nervous system, which can be caused by a variety of substances, and may include symptoms such as headache, fatigue (often extreme), dizziness and lightheadedness, sleep disturbances—both insomnia and somnolence—memory impairment, poor concentration, and brief attention span. Moreover, irritability, change in personality, and sexual disturbances can also be manifestations of central nervous system dysfunction.

One group of substances which are of particular interest in this regard is the widely used organic solvents, now almost ubiquitous in modern industry (25), which include benzene, toluene, xylene, methyl-ethyl ketone (MEK), trichloroethylene (TCE), methylene chloride, n-hexane. Although the nonspecific symptoms described are quite common in many general medical diseases, the need to consider the work environment is present when such symptoms occur. In fact, recent epidemiological investigations of workers exposed to solvents give credence to the clinical impression that this might be a problem of much greater dimensions than previously realized; of particular concern are the long-term effects of solvents characterized as "organic mental syndrome." The workup of such patients often requires both neurological and neuropsychiatric evaluation including examination with psychometric tests (26).

The central nervous system of the developing child is more sensitive than the adult CNS to certain environmental agents; the behavioral effects caused by lead are of particular concern and have become a major public health issue in the United States (27). Federal lead screening programs have identified tens of thousands of children with elevated blood lead levels, possibly associated with effects on the central nervous system. These often manifest themselves in poor performance, decreased attention span, and hyperactivity, known as "minimal brain dysfunction" (28). However, abnormalities in psychometric tests have also been reported in adults occupationally exposed to lead (29).

Although the CNS symptoms caused by some compounds are nonspecific, attention should be focused on other organs that might be affected by the same compound; some of the organic solvents, for example, can cause liver damage or peripheral neuropathy as well (30). Unfortunately, clinical biochemistry tests currently available to identify liver damage are also nonspecific, though the concomitant occurrence of CNS symptoms and liver dysfunction should alert the physician to possible occupational exposure to solvents.

A combination of both CNS and peripheral nervous system abnormalities have been reported particularly for three organic solvents: n-hexane, MEK, and carbon disulfide (CS_2). In these instances nerve conduction velocity studies can be useful (30).

Much evidence exists indicating a relationship between leukemia and benzene (31, 32). However, nonspecific hematologic changes, such as anemia and leukopenia, can also be observed in persons exposed to benzene. While these findings are not necessarily predictive of ensuing malignant disease, such nonspecific hematologic abnormalities should alert the physician to consider the work environment. Avoidance of further benzene exposure can lead to reversal of hematological changes and avoidance of leukemia. Close medical surveillance can make early diagnosis possible, should leukemia occur.

Importance of Occupational History. One of the most important diagnostic assets in occupational medicine is a thorough occupational and environmental history, which can both facilitate diagnosis and expedite appropriate therapy. It should be emphasized again that exploring the patient's work environment in detail does not mean accepting a job title or job designation as an answer; it is necessary to define particular exposures and contacts. In addition, recording the patient's own association of symptoms with exposures at the work site is often very useful and may give a clue to the causative agent(s).

Since many occupational and environmental diseases do not become clinically manifest until several decades after first exposure, a lifetime occupational history should be the rule. Even a brief exposure, sometimes during temporary employment such as a summer job or a "second job" lasting for only a few weeks, can be extremely important. Often the patient does not recall such brief exposure until the persistent physician probes for this particular detail. As an illustrative example, we encountered a patient whose occupation, at the time of the examination for a pleural mesothelioma, did not include any occupational exposure to asbestos or any other industrial agents; he was a white-collar worker. However, careful review of his occupational history revealed that he had worked in a shipyard 35 years ago, during a 5-week summer vacation while in college—the exposure, because of its brevity, was insignificant to the patient. The disease-causing potential of such short exposures must be recognized by the practicing physican. Short-term exposure with subsequent long-term effects has been documented in epidemiological studies (33).

In addition to the patient's own occupational history, it is sometimes important to inquire about the occupations of family members, especially those of parents. Industrial agents such as inorganic lead, beryllium, and asbestos have all been shown to cause disease when carried home by the worker on contaminated clothes. The finding of an elevated blood lead level in a child who does not live in a typically high-risk area (dilapidated, inner-city housing) should call attention to possible transmission of an occupational hazard from one of the child's parents. There is evidence of increased lead absorption in children of battery workers and secondary lead smelter workers (34, 35). In extreme cases, several members of a family can be affected by an occupational disease. One of us has cared for a 30-year-old patient with mesothelioma whose parents died of asbestos-related diseases, the father of lung cancer and asbestosis and the mother of mesothelioma (36). The patient had experienced the disease-inducing exposure as a small child, perhaps in her infancy, which explains the young age at which the mesothelioma developed.

The occupational history should also explore the nature of the patient's residence and its proximity to industrial enterprises. Living near a mine or quarry, a metal smelter or shipyard, can be associated with hazardous exposures from emissions. The storage ground for refuse or byproducts from various industrial processes occasionally serves as the playground for children living in the vicinity. Halogenated hydrocarbons such as polychlorinated biphenyls (PCB), lead items, and asbestos air pollution can pose significant health hazards to both children and adults (37–39).

In addition to the regular work and living environment, there is also the possibility of contact with hazardous materials through hobbies. Whether arts and crafts is a primary occupation or a hobby, many art studios are located in the home, where industrial hygiene standards are usually inadequate. The use of color pigments containing lead compounds, chromates, and cadmium entails potential exposures (40). Stained-glass making can be associated with significant exposure to lead; woodworking and painting often require the use of lacquers, solvents, and thinner, whose CNS effects have been referred to above.

The home environment itself should also be the subject of careful review in the occupational and environmental history. Materials used in the construction and insulation of a building can cause adverse health effects. In addition to the described effects of undue exposure to airborne asbestos, which is commonly used as an insulation material, attention should be given to the adverse health effects related to other modern insulation materials such as the widely used urea formaldehyde foam (41). Formaldehyde has been shown to leach for many months after installation. It has been implicated in a clinical syndrome characterized by allergic manifestations of the skin and the respiratory tract as well as CNS symptoms. It is estimated that 500,000 dwellings in the United States contain this form of insulation material. Because of the large number of cases reported with urea formaldehyde-related health effects, the use of this compound has been banned in several states in the United States (41).

Home repair, often done by the owner himself or herself without the assistance of professional workers, should also draw the attention of the examining physician. Removal of old, lead-based paints with a rotating tool or by the use of a heat gun can generate significant levels of lead in the air. In some cases this has caused overt lead poisoning (42). The physician must explicitly ask about hobbies other than do-it-yourself maintenance work, since most of these patients have regular occupations unrelated to lead exposure. Another example of hazardous home repair is the use and sanding of dried asbestos-containing spackling and taping compounds (43). Dry-wall construction workers using such materials have been found to have asbestos-related diseases. Because of increased public concern, asbestos was discontinued in these compounds in 1977.

In the context of the home environment as an important nonoccupational source of exposure, one should notice some reports that impaired pulmonary function among children is associated with the smoking habits of their parents (44).

Diagnosis: Specific Effects

Although signs and symptoms are not unique for occupational diseases in general, for some diseases the clinical picture and related diagnostic tests can be quite specific.

For example, Raynaud's phenomenon of the hands is associated with exposure to vinyl chloride (45) or the use of vibrating tools (46).

A patient who consults a physician for intermittent attacks of crampy, abdominal pain associated with constipation lasting for several days should arouse suspicion of lead poisoning (47).

Long-lasting acne lesions in an adult at body locations where juvenile acne does not occur, such as the thighs, abdomen, or behind the ears, should alert the physician to exposure to halogenated hydrocarbons, such as polychlorinated biphenyls (PCBs) or the more toxic contaminants, the polychlorinated dibenzofurans (PCDFs) (48).

One of the most toxic compounds known, tetrachloro-dibenzo-p-dioxin (TCDD), has been implicated in several industrial accidents around the world. Both workers and residents living in the vicinity of factories where the accidents occurred have shown dermatological problems with acne as the most prominent feature (chloracne) (49). The presence of cysts is a diagnostic feature which can assist the physician in differentiating between this form of acne and juvenile and other types.

Other characteristic, often pathognomonic diagnostic findings are:

for asbestos exposure: chest x-ray showing pleural thickening, calcification, and plaques on the diaphragmatic surface is virtually pathognomonic. The parenchymal changes associated with asbestos-induced disease manifest themselves as irregular opacities (50); a chest x-ray exhibiting rounded opacities and mediastinal lymph nodes with the appearance of "egg shells" makes the diagnosis of silicosis likely.

for lead poisoning: changes in porphyrin metabolism are quite specific. Elevated erythrocyte protoporphyrin either as "free" erythrocyte protoporphyrin (FEP) or zinc protoporphyrin (ZPP) is often diagnostic (51, 52).

for organophosphate pesticide poisoning: measurement of acetylcholinesterase in both serum and erythrocytes is specific. As mentioned earlier, exposure to neurotoxic agents, such as the organic solvents, should prompt both neurologic and neuropsychologic evaluation, and the use of such methods is now being applied more often in the detection of occupationally related disorders affecting the nervous system (54).

Fertility problems in males may be revealed by semen analysis, and both azoospermia and oligospermia have been found in workers exposed to the nematocide dibromochloropropane (DBCP) (55).

Treatment and Prevention

Perhaps in no other field of medicine are diagnosis, treatment, and prevention so strongly interrelated as in occupational medicine. For some occupational diseases, for instance the acute poisonings, specific treatment is available. Chelation therapy might be resorted to in cases of metal poisoning (56), and the use of atropine and PAM-chloride are specific antidotes used in organophosphate poisoning (57).

Treatment of Choice: Prevention. But the treatment of choice for occupational disease is prevention. A key issue in preventing occupational diseases is the optimal design of the industrial environment, in other words avoidance of exposure. This applies not only to exposures per se, but also to the adaptation of work procedures to human physical characteristics (58). This calls for joint efforts between physicians and specialists in ergonomics and industrial hygiene. The widespread use of video display terminals can cause neuromuscular symptoms among operators and it has been suggested that these symptoms are an ergonomic problem rather than a problem of exposure to nonionizing radiation (59). Carpal tunnel syndrome, for example, can be prevented by the proper design of hand tools. In many instances the proper design is achieved only after cases of occupational diseases have already occurred. It is inconsistent with good preventive medical practice to correct the environment after the onset of disease, when the potential for such disease is already known. In a historical perspective, preventive measures thought to have controlled a problem have sometimes been proven to be inadequate. Although the development of environmental standards has contributed to the control of many occupational diseases, such standards do not always insure against the development of untoward effects. For example, the current U.S. asbestos standard of 2 f/cc will probably narrow the spectrum of asbestos-related diseases, particularly with regard to decrease of severe asbestosis; but there is good reason to believe that this standard will not suffice for prevention of asbestos-related neoplastic diseases (lung cancer, mesothelioma, gastrointestinal and other cancer). Again, the importance of prevention should be emphasized in view of our limitations in treating such diseases.

In other instances, the development of new standards has been prompted by additional scientific information which provided evidence for significant biological effects at levels that were previously considered "safe" (60). The lowering of the lead standard in the United States was primarily based upon information which indicated that nervous system dysfunction may occur at the levels of the previously recommended values (61).

Early Detection. The early detection of occupational diseases can be considered the second most important preventive approach. However, we are seriously limited in achieving this goal with currently available conventional diagnostic methods. In fact, this state of affairs is one of the most urgent problems for researchers in the field of occupational medicine today. Some means are, of course, available to the practicing physician for the early detection of disease, ranging from tests for occult blood in stool to measurement of carcinoembryonic antigen (CEA), pap smear, and urinalysis. The measurement of transfer RNA breakdown products in the urine has recently received attention as a possible means for early diagnosis of cancer (62). Whether environmentally induced immunosuppression is a predictor of cancer development is now a subject for intense study, and may have important practical clinical implications (63).

Nutritional modulation of the effect of environmental toxicity may prove to be useful, since some variations in host response to toxic effects have been related to nutritional status. For example, the toxic effects of lead might be enhanced in persons with calcium and iron deficiency (64).

Recent suggestions concerning the reversal of risk of lung cancer after high intake of Vitamin A are of interest (65).

The importance of educating the patient about preventive measures such as habits and life style cannot be overemphasized. As noted, discontinuing of smoking will significantly lower the risk of lung cancer development in workers exposed to asbestos (18). In fact, this is currently the most important clinical action that can be taken to prevent lung cancer in general, but especially in persons at particularly high risk, such as asbestos workers.

Legal, Economic, and Social Ramifications. The diagnosis of an occupational disease often touches upon aspects of a person's life not usually affected by a general medical diagnosis. In addition to the importance of correct medical handling of a patient with an occupational disease, the establishment of a cause-effect relationship may have important legal and economic implications; thus, the physician's role is very important (66). Usually there is no requirement to provide unequivocal proof of the cause of the disease in question, and "reasonable medical evidence" is often sufficient to obtain compensation or other economic recompense that may be awarded to the patient or the family by a court.

It should be stressed that simple preventive measures, such as those outlined above, may, in fact, be extremely difficult to achieve in occupational settings. Environmental disease is often at the interface between the medical practice and the changing industrial world. The consequences of a patient's illness extend from the patient to the physician as well, and may require the physician's interaction with members of the family, employers, unions, insurance companies, unemployment agencies, disability institutions, workers' compensation boards, and other social institutions.

The ramifications of a diagnosis of an occupational disease can be far-reaching, and the physician handling environmental and occupational problems may find himself dealing with issues outside the traditional realm of physician's activities. Nevertheless, the physician remains the key figure in ultimately conquering this worldwide public health problem through skill in early detection and diagnosis, and patience in teaching the public the questions they must ask, so that an unsafe environment can be avoided.

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Submitted for publication March 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

The Youth of Geriatrics

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Abstract

Geriatrics is generally considered a discipline of recent origin. In fact, it has been fashioned over the centuries by the customs and pressures of society. Old age was once just an occasional individual experience and a not infrequent family problem. Due to the contemporary population explosion in the senium, it has also become a socioeconomic phenomenon of prime national importance. This paper is an attempt to recognise and follow the sequence of some cultural and medical factors that have shaped the development of present-day geriatrics.

The Fifth Commandment reminds us that concern for the elderly is not a recent social phenomenon. Fifteen hundred years before Christ, papyrus texts (Papyrus Ebers and the Edwin Smith Surgical Papyrus) contained sections devoted to the treatment of wrinkles, baldness, and debility, with one "for Transforming an Old Man into a Youth of Twenty" (1, 2).

In the last decade, the surge of interest in the public health aspects of advanced age has led to the establishment of the National Institute on Aging and special departments in hospitals and medical schools. Although the term "geriatric" is a recent addition to the functional vocabulary of the nation, the later years of life engaged the attention of previous societies, long ago.

Hippocrates. In the fifth century BC, Hippocrates' treatment of old age was largely hygienic. He prescribed a regimen of temperance in diet and activity with planned exercise and recreation. This has been the basis of all systems of geriatric care ever since. His aphorisms are sprinkled with empirical gems about disease in the aged (3).

Cicero. The first major treatise on old age was written by the immortal Marcus Tullius Cicero in 44 BC, a year before his death at the hands of Mark Antony's assassins (4). Cicero was then in his sixty-third year. His beloved daughter, Tullia, had just died. His career had been ended by the triumph of his political enemies. His young wife was estranged. Despite this crushing burden of misfortunes, his *De senectute* resolutely declares that old age itself is a disease that can be warded off by courage, industry, frugality, and pride of accomplishment. As in the composition of his *Republic,* Cicero adopts the format of an imaginary dialogue held in the year 150 BC. The protagonist is the distinguished Marcus Porcius Cato, then in his eighty-fifth year, discussing old age with two young men of note.

Cato, busily engaged in writing a history of early Rome, had enjoyed a brilliant career as soldier, politician, consul, and statesman. His interlocutors express amazement at his physical and mental powers. In reply, he denies these as unique gifts and cites several examples of great accomplishment by others at an advanced age. Cicero has him express the fortitude needed by the elderly: "I follow Nature as the best of guides, and obey her as a god; and since she has fitly planned the other acts of life's drama it is not likely that she has neglected the final act as if she were a careless playwright" (5).

Horace. Then, as now, not everyone shared this constructive view of the later years. Horace, the satiric poet and contemporary of Cicero, wrote, in the translation by John Conington (6):

> Grey hairs have many evils without end;
> The old man gathers what he dare not spend
> While, as for action, do what he will,
> 'Tis all half-hearted, spiritless and chill;
> Inert, irresolute, his neck he cranes
> Into the future, grumbles and complains,

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Extolls his own young years with peevish
praise,
But rates and censures these degenerate days.

Galen. The term "gerontology" was introduced by Galen in the second century AD (7). It is more comprehensive than "geriatrics" in that it goes beyond physical, mental, and emotional problems to include the social and economic aspects of aging.

Galen was born in 1311 AD at Pergamum on the coast of Asia Minor. At the time, this city—with its famous library—was still basking in the afterglow of the grandeur that was Greece. Parchment had been invented there, about 180 BC. Galen's father, Nicon, was an architect, mathematician, and astronomer. He educated his talented son by sending him to the leading scientists and physicians of that period. Galen finally went to Rome in 164 AD. He ultimately became physician to the Emperor Marcus Aurelius and his son, Commodus. After a brilliant career in the imperial city, Galen returned to Pergamum, devoting the remainder of his life to his famous sanatorium, remains of which still stand, and to the compiling of those voluminous medical works which became the basis of medieval medicine.

One section of his *Hygiene* is titled "Galen's Gerontology." After several didactic chapters, he presents the case histories of two old men, in an analytic attempt to explain their longevity (8). He shows that they shared the same diet of toasted bread, honey, vegetables, fish, fowl, and wine, all eaten sparingly. Their lives were scheduled into periods of exercise, massage, rest, and recreation. They were cared for in considerate, skilled fashion.

Galenic medicine remained dominant until the end of the sixteenth century because of the efforts of sagacious and industrious Arab physicians of the eleventh and twelfth centuries AD. They annotated Galen's manuscripts and translated them into Arabic. These were later transposed into Latin and the vernacular in western Europe.

Roger Bacon. One of the great intellects of the human race was sufficiently unfortunate to be born in the thirteenth century. Roger Bacon, a Franciscan friar, was educated at Oxford, and taught there and at the University of Paris (9). He was constantly in difficulties with the church authorities because of his rebellious attitude, made more formidable by profound learning and an original bent of mind. Except for the short period following the ascendancy of his friend and protector, Clement IV, to the papal throne in 1265 AD, he spent years in seclusion and confinement. His Latin manuscript "The Care of Old Age and the Preservation of Youth" was not printed until 1590 AD and was not translated into English until 1683 (10).

Bacon followed Cicero and Galen in viewing old age as a diseased state and not simply a chronologic phenomenon. He states, "From these three things, namely infection, negligence and ignorance, the natural heat, after the time of Manhood is past, begins to diminish and its diminution and intemperature doth more and more hasten on. Whence the heat by little and little decreasing, the accidents of old age come on" (11).

Zerbi's *Gerontocomia.* The next landmark in geriatrics appeared in Rome in 1489 AD with the publication of Gabriele Zerbi's *Gerontocomia*. We owe its recognition and translation to the late Dr. Frederic D. Zeman of New York, pioneer geriatrician and historian (12).

Zerbi, a native of Verona, led an adventurous life. He taught philosophy at Padua and Bologna before being called to Rome. There, he committed the egregious error of calling Pope Sixtus IV ignorant. He fled back to Padua, where he was promptly accused of stealing two silver vases. Once more, he returned to Rome, where the *Gerontocomia* was published. After a short stay, an attractive financial offer led to his return to the intellectual life of Padua (13).

In 1505, the Turkish pasha appealed to the Doge of Venice, Andre Gritti, for the services of a physician capable of relieving him of some of his physical ills. Zerbi accepted this important mission and embarked on the long and hazardous journey to Constantinople. Initially, the pasha improved and loaded Zerbi and his son with valuable gifts. Shortly after their departure, the pasha died. His servants thereupon pursued Zerbi and caught up with him in Dalmatia. He and his son were slaughtered.

The *Gerontocomia* lists two phases of old age: a latency period and the obvious phase, marked by debility and the manifestations of senescence. Since there are chronologic limitations to human existence, the treatise is aimed at the retardation of old age by traditional methods. The basic philosophy is hygienic, the adoption of a life style that avoids all types of mental and physical stress. This is presented in 57 chapters covering every detail of the ideal environment for the elderly.

Zerbi describes the design of the buildings needed to properly house his wards. The climate, amount of sunlight, elevation, and drainage of the grounds are all considered. Appropriate facilities for exercise, bathing, eating, and sleeping are planned. Music, books, and the drama were to be available, as in Galen's time. Zerbi would be shocked, indeed, to visit one of our nursing homes five hundred years later.

In addition to providing a standard system of geriatric care, Zerbi was the first to concern himself with the type of person that would minister to those dwelling in his homes for the aged. These specialists would bear the title of "Gerontocomus." Their qualifications and duties were set forth: "He should be humane, of advanced age, familiar with medicine, frugal, moral, experienced, religious, clean, moderate in eating, of good habitus, well groomed, without body odors or excessive perspiration. He should inspect the urine of people daily" (12).

In his review in *The Journal of Mount Sinai Hospital*, Dr. Zeman presented the *Gerontocomia* as a landmark in the history of geriatrics. It summarized and organized all previous experience, providing a philosophic and empiric basis for what was to follow.

Faust: Rejuvenation. In the sixteenth century, the ancient Egyptian idea of rejuvenation surfaced in the form of the Faust legend.

There was an actual Johannes Faustus who was an alchemist and self-styled necromancer (14). He lectured in magic at the University of Cracow, was sufficiently well known to be sent for by King Frances I of France, and died in 1539. The first "Faust" book describing the legendary 24-year pact with Mephistopheles in which Faust bartered his soul for satisfaction of his erotic desires was published in Frankfurt in 1587. This allegorical presentation of the conflict between an aging man's lust and his moral responsibilities gave rise to Christopher Marlowe's play, Goethe's poetic drama, and Gounod's opera. (The clinical aspects of rejuvenation are discussed below in the appropriate time-frame.)

At the dawn of the seventeenth century, old age was still considered an individual experience, occasionally a family problem, a questionable reward for those few who survived life's earlier vicissitudes. A contemporary playwright (15) summarized the situation:

> And so he plays his part. The sixth age shifts
> Into the lean and slipper'd pantaloon.
> With spectacles on nose and pouch on side,
> His youthful hose, well saved, a world too wide
> For his shrunk shank; and his big manly voice,
> Turning again toward childish treble, pipes
> And whistles in his sound. Last scene of all,
> That ends this strange eventful history,
> Is second childishness and mere oblivion,
> Sans teeth, sans eyes, sans taste, sans everything.

The Science of Demography. Then, quite suddenly, the science of demography was born and the senium became a socioeconomic phenomenon. In 1662, John Graunt, gentleman haberdasher, fellow of the Royal Society of London, published his "Natural and Political Observations . . . upon the Bills of Mortality (16). These "bills" were weekly statements entered in each parish register beginning in the year 1538 by order of King Henry VIII. All weddings, christenings, burials, epidemics, and other vital matters were recorded. By 1603 the bills were being kept regularly. In 1625, the Archbishop of Canterbury assigned a printer to compile and publish the accounting annually the Thursday before Christmas.

Graunt's essay opens with an index which is an annotated listing of his tables of statistics drawn from the bills of mortality. He estimates life expectancy at all ages, noting the causes of death and the yearly variation thereof. His "table of casualties" is drawn up with the various diseases and types of trauma listed in the ordinate and the years from 1607 to 1629 strung along the abscissa. He analyzes all the data with regard to age and sex, population densities related to housing, the influence of medical care, and the differences between those parishes grouped in London and those outside its walls (Fig. 2).

A contemporary and life-long friend of Graunt, William Petty, shares responsibility for the origin of demography and in fact has been suspected of being the actual author of Graunt's essay. Petty, a talented physician, mathematician, linguist, and businessman, contributed a series of important papers to the Philosophical Transactions of the Royal Society between 1661 and his death in 1687. In these he laid the foundations of political economy (17), introducing the concepts of national income, cash flow, tax policy, and the fiduciary aspects of life expectancy (18).

This new discipline and social outlook was further enhanced by the famous astronomer and mathematician Edmond Halley. In 1693, he presented to the Royal Society his "Estimate of the degrees of the Mortality of Mankind; drawn from curious tables of the births and funerals at the city of Breslau (Silesia), with an attempt to ascertain the price of Annuities upon lives" (19). His mathematically deduced formulae for life ex-

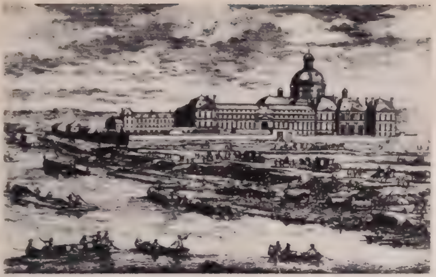
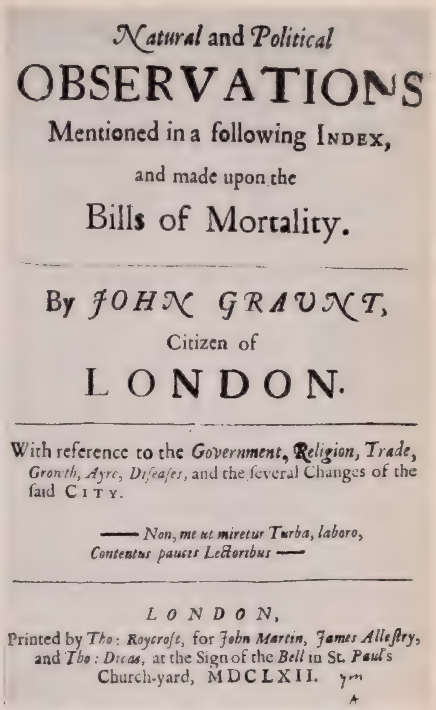


FIG. 1. La Salpetriere Hospital toward the end of the seventeenth century. Reprinted from Georges Guillain and Pierre Mathieu, *La Salpetriere. Courtesy of the New York Academy of Medicine Library.*

pectancy at any age established a socioeconomic concept of the aging process which was not fully understood by the founders of Social Security in this country. Our current political turbulence in this matter attests to that.

A book entitled *Human Longevity* was published by James Easton of Salisbury in 1799 (20). In it he lists the name, age, place of residence, and year of death of all persons recorded as having reached the age of 100 years since 66 AD (Fig. 3). His compendium included an alphabetical index of the long-lived as well as a biographical paragraph or two whenever sufficient information was available. Easton's table of life expectancy for males in England at the end of the eighteenth century reports that, for every hundred born, 50 die before their tenth year, 20 before the twentieth, 10 before the thirtieth, 6 before the fortieth, 5 before the fiftieth, 3 before the sixtieth; only 6 (of 100) survive beyond that age. He strikes this sardonic note: "It is not the rich and the great, not those who depend on medicines, who become old; but such as use much exercise, are exposed to the fresh air, and whose food is plain and moderate, as farmers, gardeners, fishermen, labourers, soldiers etc; and such men as perhaps never employed their thoughts on the means which have been used to promote longevity" (21).

Clinical Geriatrics and Hospital-Based Medicine. The foundation of modern geriatric medicine was laid by Burkhard Wilhelm Seiler, a German pathologist, in 1800. His monograph *The Anatomic Changes of Old Age* emphasized the fact that people died of disease, not of "old age." He reviewed the morbid anatomy of the elderly sick with appropriate microscopic and chemical examination. The remnants of Galenic medicine were finally discarded by the scientific objectivity of the nineteenth century (22).



Natural and *Political*
OBSERVATIONS
Mentioned in a following INDEX,
and made upon the
Bills of Mortality.

By *JOHN GRAUNT*,
Citizen of
LONDON.

With reference to the *Government*, *Religion*, *Trade*, *Growth*, *Ayre*, *Diſeaſes*, and the ſeveral Changes of the ſaid CITY.

—— Non, me ut miretur Turba, laboro,
Contentus paucis Lectoribus ——

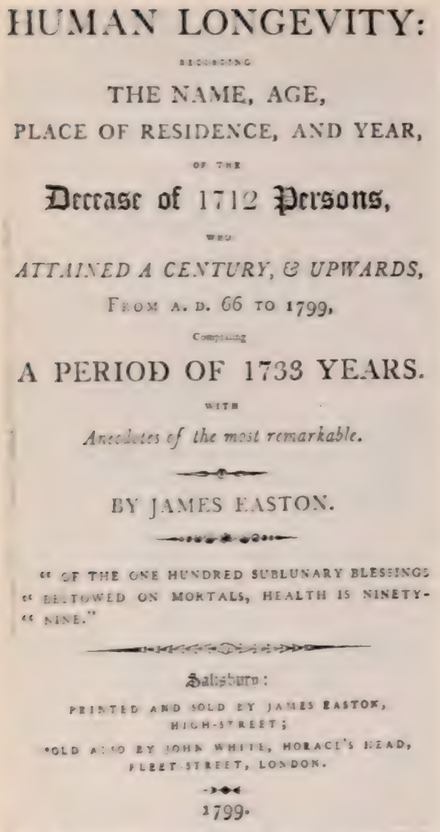
LONDON,
Printed by *Tho*: *Roycroft*, for *John Martin*, *James Alleſtry*,
and *Tho*: *Dicas*, at the Sign of the *Bell* in St. *Paul's*
Church-yard, MDCLXII.

FIG. 2. Frontispiece, John Graunt, *Natural and Political Observations made upon the Bills of Mortality* (1662). *Courtesy of the New York Academy of Medicine Library.*

In 1839, clinical geriatrics was founded by Carl Friedrich Canstatt, who was trained at the famous Charite Hospital in Berlin. His *Diseases of Old Age and Their Treatment* appeared in two volumes (23). The first dealt with the morbid anatomy and physiology of the elderly, including chapters on nutrition, circulation, excretion, and respiration. The second volume was devoted to specific diseases.

At this time, the hospital became the center of medical activity, the arena for teaching and research. In the development of geriatrics two became preeminent, the Chelsea Royal Hospital in London and the Salpetrière in Paris.

The Chelsea Hospital building began in 1610 as the King James College of Theology. (24). It became a prison in the English Civil War, then a riding academy, and was given to the Royal So-



HUMAN LONGEVITY:
RECORDING
THE NAME, AGE,
PLACE OF RESIDENCE, AND YEAR,
OF THE
Decease of 1712 Persons,
WHO
ATTAINED A CENTURY, & UPWARDS,
FROM A. D. 66 TO 1799,
Comprising
A PERIOD OF 1733 YEARS.
WITH
Anecdotes of the most remarkable.

BY JAMES EASTON.

" OF THE ONE HUNDRED SUBLUNARY BLESSINGS
" BESTOWED ON MORTALS, HEALTH IS NINETY-
" NINE."

Salisbury:
PRINTED AND SOLD BY JAMES EASTON,
HIGH-STREET;
SOLD ALSO BY JOHN WHITE, HORACE'S HEAD,
FLEET-STREET, LONDON.

1799.

FIG. 3. Frontispiece. James Easton. *Human Longevity* (1799). *Courtesy of the New York Academy of Medicine Library.*

ciety by Charles II. It was repurchased by the Crown and presented to the king's favorite, Nell Gwynne, who suggested that it be remade into a hospital "for the relief of decayed soldiers." The Chelsea Hospital was finally completed in 1702 and served thereafter for the care of veterans and pensioners.

The Salpietrière was founded by Louis XIV in 1656 (25). It has served as an almshouse-pest-house-insane asylum-hospice-hospital ever since (Fig. 1). It was here that the great French clinicians of the nineteenth century did their pioneering work in medicine, neurology, and psychiatry. Outstanding in this array of talent was the great neurologist, capable pathologist, and brilliant internist Jean-Martin Charcot (1825–1893). He was a gifted artist, as well, and wrote an essay on disease in art. (26). His vast experience at the Salpetrière culminated in the publication of *Clinical Lectures on the Illnesses of the Elderly and Chronic Disease* in 1867 (27), a systematic study of the afflictions of old age emphasizing pathology. It had a profound effect on the profession and served as a model for numerous monographs in France and other countries.

In 1886 Emile Demange, who had set up a geriatric service at the Saint Julien Hospital in Nancy, reported on his experiences there, emphasizing circulatory system disease in advanced life and the significance of arteriosclerosis (28).

In 1895, Dr. Jules Boy-Teissier published his bedside lectures at his geriatric service at the Sainte Marguerite Hospital in Paris. He described the aging of individual cells and connective tissue as well as disease syndromes and senescence (29).

In 1908, the Nobel Prize for Medicine was awarded to Elie Metchnikoff, a Russian-born research scientist at the Pasteur Institute working primarily in bacteriology. His popular book *The Prolongation of Life* (30) discussed the disharmonies of the various body systems leading to premature senescence from the anthropological viewpoint.

He was concerned with intestinal putrefaction caused by rich diet, overindulgence in alcohol, and the ingestion of food contaminated by inimical bacteria. He advocated the consumption of buttermilk and yogurt to foster the growth of those microbes causing lactic acid fermentation to inhibit putrefaction. If tissue poisoning due to the absorption of bacterial toxins from the large intestine could be avoided, a state of "orthobiosis," or prolonged active old age, could be attained.

Because of the publicity attending his ideas, the public became vibrantly aware of the horrors of constipation. Colonic irrigation parlors sprouted. The landscape was desecrated by huge signs indicating the willingness of purveyors of patent cathartics to save the costive populace from premature death.

Revival of the Rejuvenation Theme. Another development in geriatrics which engaged the attention of the public was the "scientific" revival of the Faust motif. It began quietly in the laboratory of the famous Charles Edouard Brown-Sequard, distinguished neurologist and successor to the great Claude Bernard as professor of experimental medicine in the Collège de France.

Brown-Sequard injected himself with an extract of animal testis, with presumptive benefit (31).

Forty years later, a triumvirate of sex enhancers gave rise to numerous press reports as rejuvenation became a popular theme of the 1920s.

Professor Eugen Steinach of Vienna was a reputable researcher in the new field of endocrinology when he became interested in the internal secretions of the testes and ovaries. His work in the laboratory convinced him that ligation of the vas deferens, the duct leading the spermatozoa away from the testis, would cause increased absorption of male sex hormone, with systemic effects of a happy nature (32). Steinach's report was promptly picked up by journalists, who ignored the fact that he was not a surgeon and had never, himself, performed this procedure on humans (33).

Even better known was Dr. Serge Voronoff, a French surgeon, who was an enthusiastic advocate of the transplantation of tissues. He reported the successful transfer of young ram's testes into old men with most encouraging results (34). He then used monkeys and apes as the donors and his name became known wide and far (35). Voronoff apparently developed a large and lucrative practice.

The third and most successful was John R. Brinkley. After a boyhood of destitution on a barren farm in North Carolina, he spent his early manhood drifting through the small towns of the South and Midwest scratching for a living. He bought a certificate from a medical diploma mill in St. Louis and thereafter always referred to himself as "doctor" (36). With this dubious document he fraudulently obtained a medical license in Kansas and, by reciprocity, in other states. In 1917, after a medical discharge from the Army Medical Corps, he located his practice at a small railroad stop, Milford, Kansas. He began transplanting "goat glands" into men of diminished virility. His commercial success, which he owed to his sheer insolence, his talent for publicity, and the incredible gullibility of the aging male, was rapid and overwhelming. He soon owned his own airplane and radio station and by 1930 was in a position to run for governor of the state of Kansas. He was a strong candidate and tried again in 1932 and 1934. Finally, enraged by the persistent surveillance of Dr. Morris Fishbein, editor of the *Journal of the American Medical Association*, during a campaign against charlatans, he committed the fatal mistake of suing his tormentor for libel. Although Brinkley brought the action in the friendly town of Del Rio, Texas, it was of no avail. The court records indicate how completely he was unmasked (37). The suit was dismissed and he died two years later.

There is no hope in the human breast as eternal as that of rejuvenation. It is conceivable that the burgeoning sciences of molecular biology and experimental pharmacokinetics may yet confront future geriatricians with cases of frenetic sexual activity in the ninth and tenth decades.

Randall and Townsend. In sharp contrast, there are two Americans who had a profoundly beneficial effect on the status of the aged in this country.

Ollie Randall returned from service with the American Red Cross during World War I to resume her professional career on the staff of the New York Association for Improving the Condition of the Poor. From the time she graduated from Brown University, she devoted herself to the plight of the aged (38). She trooped around the country for years attending professional, business, and labor conventions on behalf of her elderly wards (39). She was instrumental in the formulation of Social Security legislation. She was one of the founders of the National Council on the Aging and received a presidential citation for her role in the first White House Conference in 1951. The evangelism of Ollie Randall was unique in its combination of fervor, intellectuality, and abiding love of humanity. She made the conscience of America aware of its responsibility to the aged.

Dr. Francis E. Townsend was an elderly retired physician leading a forlorn existence in Long Beach, California, in 1933 after a hard life of toil and struggle in the Midwest. The Great Depression found him in grave financial straits. In desperation, he conceived a plan whereby the federal government would pay $200 on the first of each month to every citizen over the age of 60 years in need of financial assistance. By law, this sum would have to be spent in that month. The plan would be financed with a federal transactions tax. Since two-thirds of all American families in 1934 had annual incomes of less than $2,000, this proposal was greeted with unbounded enthusiasm by millions of the elderly. By 1935, there were seven thousand local Townsend clubs and a national convention was held in Chicago. The thin, ascetic, deeply religious physician had become a Messiah of the old and the impoverished. The meteoric career of Francis Townsend, his political importance in the presidential election of 1936, and his subsequent disappearance from the national scene are related by Professor David Bennett of Syracuse University in his *Demagogues in the Depression* (40).

The Townsend episode is of historic importance. It brought a new dimension to gerontology. It meant the end of the long tradition of the elderly begging for alms from local authorities and eleemosynary institutions. The future of geriatrics was to be largely determined by a new political power quite prepared to take its place beside the financial, labor, and farm lobbies in Washington, D.C.

Contemporary and Future Possibilities. The status of the aged in our society has numerous facets reflecting the medical, social, economic, and political vagaries of the environment. While an instructive and well-written literature on this subject has accumulated in the last twenty years, Dr. Robert N. Butler's *Why Survive? Being Old in America* can serve as the bible of contemporary gerontology (41). It is compassionate, authoritative, and well-documented.

In the absence of national disaster, manmade or natural, continued medical success in the treatment of chronic sickness matching that already accomplished in epidemic and infectious disease will result in a population explosion of the senium. Even if Metchnikoff's concept of a prolonged state of functional health in advanced age is generally attainable, difficult social and economic adaptations will be necessary to accommodate this gerontologic serendipity.

Finally, will Malthusian factors come into play as longer life spans lead to increase in population with widening age spectrums? Of what avail to foster a longer, happier life span in this country in contrast to the demographic anarchy of the multiplying peoples of Asia, Africa, and Latin America?

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Submitted for publication March 1983

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

A Quantitative Skin Touch-Retouch Test: A Fluorescence Method

FARRINGTON DANIELS, JR., M.D., M.P.H., STEVEN R. ROTHSTEIN, M.D., AND STEVE BLUM, PH.D.

Abstract

A quantitative sensorimotor test is described. The examiner touches a spot on the skin with tetracycline in a rapidly evaporating solvent. The patient, who has not seen the application, then tries to relocate the spot with a visible marking pen. Under illumination by Wood's light, the distance between the fluorescent stimulus and visible response marks is a measure of accuracy. Among the commonly used clinical tests of sensation, only two-point discrimination yields a numerical score, but this test requires repeated administrations to reach an endpoint. The fluorescence test is simple and requires only one administration; results can be read as a linear dimension. It offers promise as a test for physiological aging and the obtunding effects of drugs or neurological defects, and can be used to follow the course of such patients. Numerical measurement as opposed to description permits comparisons between persons and by disease, is usable across both time and distance, and can provide the basis for mathematical and statistical analyses.

Weber (1), in 1852, was probably the first of several (2, 3) investigators to use a sensorimotor test in which the patient attempted to retouch or otherwise identify a point on the skin touched by the examiner. Various methods have been employed to keep the patient from seeing the examiner's touch. Our interest in the subject was aroused by two considerations. First, in studying the effects of sunburn and 8-methoxysporalen photosensitization of human skin, Daniels and Bergeron (4) noted that none of the commonly used clinical sensory testing methods produce quantitative assessments, with the exception of the two-point discrimination test. Second, in a personal conversation in 1964, Prof. Graham Weddell (5) of Oxford told one of us (F.D.) that in his experience studying leprosy, the touch-retouch technique was the most sensitive indicator of peripheral nerve loss.

It occurred to one of us (F.D.) that if the examiner stimulated with a fluorescent probe invisible to the subject, and if the patient made an estimate of the stimulus point with a regular pen, measurement of the difference under Wood's light ("black light") would give linear measurements suitable for analysis. An advantage over the two-point discrimination test is that the fluorescence test is a single test rather than a closing in on a subjective endpoint.

This report is preliminary confirmation of the usefulness of the approach suggested.

Methods

Fifty-two volunteer subjects among the patients in the Dermatology Clinic at The New York Hospital were studied. They were all free of neurological disease or of skin disease in the tested areas. The subject both closed his eyes and turned his head away while the examiner (S.R.) touched a single spot with a cotton-tipped applicator of tetracycline. Topicycline is a commercial preparation of tetracycline in a rapidly evaporating solvent, sold for acne treatment. The preparation comes as a powder to dissolve in the solvent, and was used double strength. Since the product is sold for use on the skin, any uncer-

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From the Dermatology Division, Department of Medicine, Cornell University Medical College, New York City, and Mount Sinai School of Medicine of The City University of New York. This study was carried out in the summer of 1979 when Dr. Rothstein was a medical student at Mount Sinai School of Medicine. Address reprint requests to Dr. Daniels at Dermatology Division, Cornell University Medical College, 1300 York Avenue, New York, NY 10021.

tainty about the safety of the dye was alleviated. The subject was then instructed to open his eyes and touch the now invisible stimulation point with a felt-tipped pen. The distance between the two spots was measured with a micrometer caliper under black light (Wood's light) illumination.

Prestrude and Johnstone (6) used similar logic in their test, in which the patient wore red glasses and a red marker was used by the examiner:

> The localization error was determined by the distance between a spot on the subject's skin touched by the experimenter with a red felt tip pen and the spot touched by the subject with a black felt tip pen in an attempt to touch the red spot. The tip diameters of the pens were 1 mm. Each subject wore red goggles which prevented him from seeing the red spot touched by the experimenter but allowed him to visually guide his localization attempts.

The spots used in our fluorescence test on the upper extremity were fingertip, middle of palm, middle of dorsum of hand, middle of ventral and middle of dorsal surfaces of the mid forearm, all areas convenient for clinical examination. Other studies were done on the lower extremities which are not reported here.

Fortunately a subset of subjects indicated that there is no difference in use of dominant or nondominant hand by the patient, although only right-handed subjects were used. No significant difference was found between right and left sides.

The spots were touched in variable order so that the subject could not anticipate the area. A table of random numbers was not used to mathematically randomize this aspect. The 52 subjects ranged in age from 17 to 78. The 15 subjects over 65 appeared to have decreased accuracy, but the sample size was considered insufficient to attempt a regression line of accuracy as a test of aging.

Results

The results are summarized in the Table.

It would appear that palm and dorsum of the hand would be logical sites for routine testing, although in suspected leprosy or other neurological disorder the test would be carried out where needed. No significant differences were found between men and women, nor between black and white subjects. The decreased accuracy as the test area was more proximal is in line with other tests. Weinstein (3) found that two-point discrimination was most accurate on the fingers, next on the face, and third on the toes.

TABLE

Errors of Localization (in cm) of Right and Left Upper Extremities

	Left upper extremity (n = 52)		Right upper extremity (n = 30)	
	Mean	SE	Mean	SE
Finger	0.24	±0.03	0.26	±0.03
Palm	0.66	±0.08	0.77	±0.08
Dorsum hand	1.12	±0.09	1.24	±0.18
Ventral forearm	1.91	±0.20	1.88	±0.27
Dorsal forearm	2.03	±0.20	1.76	±0.23

This simple test, which converts a sensorimotor response into easily measured numbers, permits quantitative evaluation of changes in a given individual, and can be used for group statistics. Among the uses we can see are the following:

1. Measuring aging. Support for this possibility is provided by the two-point discrimination studies of Gellis and Pool (7) and Kayahan et al (8).
2. Evaluating and measuring changes in time in leprosy and other nerve disorders (9).
3. Evaluating and following the degree of obtundation in patients on various therapeutic and "recreational" drugs.
4. Measuring sobriety, although this would be complicated by the fact that the control tests would have to be done after the subject sobered up.

Summary

We believe that the potential usefulness and simplicity of the test warrants presenting in this preliminary form. The red glasses technique of Prestrude and Johnstone would be an advantage where testing must be done in a lighted area, although supplying clean glasses to large numbers of subjects might be a nuisance. The fluorescence method would be of particular use in dermatology and pediatric clinics, where black light (Wood's light) is already used for examining patients with fungus infections and pigmentary disorders.

Acknowledgments

We are indebted to Dr. Patricia Myskowski for suggesting Topicycline as the fluorescent marker.

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Submitted for publication June 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Celiac Plexus Block: An Overview

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Of all the symptoms of pancreatic disease, the one that is most disabling to the patient is pain (1). As the pain becomes more severe it becomes increasingly difficult to control. Frequently, patients with pancreatic pain spend most of their time in bed in a semistupor under the influence of narcotics. If they have pancreatic carcinoma their pain escalates despite increasing doses of narcotics, while their families and friends helplessly watch their slow demise. After celiac plexus block, which is itself safe, a patient may die of the disease or other cause—but the death can be painless, and some who undergo this procedure even return to work and lead a normal life.

The cause of pancreatic pain is still in doubt, but it seems that pain may arise from complete or incomplete obstruction of the pancreatic duct with distension, inflammation, and infiltration of pancreatic connective tissue capillaries or afferent nerves. Pain may be somewhat relieved by body flexion. It is a deep-seated pain in the epigastrium, radiating to the back.

Of the four methods employed for the control of pain—surgery (resection and bypass procedures), drugs, chemotherapy and radiotherapy, and nerve blocks—we deal here only with the last.

Anatomy. The celiac plexus lies around the origin of the celiac artery (2). Posteriorly it is bounded between the crura of the diaphragm and the first lumbar vertebra; laterally by the kidneys and suprarenal glands; and anteriorly by the pancreas.

The celiac plexus consists of sympathetic and parasympathetic afferents from viscera and limbs. Even though vagal fibers are present, this is predominantly a sympathetic plexus. It also receives fibers from the greater and lesser splanchnic nerves arising from T7 to T12.

The greater (T7-T10), lesser (T10-T11), and least (T12) splanchnic nerves feed into the two semilunar or celiac ganglia, in reality the major right and left portions of the celiac plexus. The right celiac ganglion lies medially and posteriorly to the inferior vena cava. It intertwines anterior to the aorta with a dense network of fibers from the left ganglion.

The left ganglion lies posterior to the pancreas and medial to the upper pole of the kidney and adrenal gland. Superiorly both ganglia lie flattened against the crura of the diaphragm.

With the presence of pancreatic tumors, the anatomy may be distorted depending upon the site and size of the tumors.

Apart from right and left celiac ganglia, there are aorticorenal ganglia just below them and branches to phrenic, hepatic, left gastric, splenic, superior mesenteric, renal, and suprarenal ganglia. Afferent fibers pass from the pancreas to the celiac plexus, then via the splanchnic nerves to T7 to T12 dorsal roots, and finally up the spinal cord to the sensory cortex (1, 3).

Indications. Celiac plexus block is indicated as a diagnostic tool, and as therapy for (a) cancer of the pancreas and pancreatitis, (b) retroperitoneal tumor or metastases with pain, or (c) chronic abdominal pain unresponsive to treatment.

Pre-block Visit. During a pre-block visit, the characteristics of the pain are noted and the side of the worst pain is determined. Informed consent is obtained after explaining to the patient what is involved in the block, what is expected and not expected of the block, and what the possible complications may be. The patient is told that the block is not a cure for the disease, but only an attempt to alleviate the pain. The patient is given no premedication, and, if possible, no pain medication, as it is preferable that there should be some pain when doing the block. Any patient receiving anticoagulants must stop taking them until the prothrombin and bleeding times are normal, or near-normal. These tests should be performed routinely on all patients un-

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dergoing nerve blocks, including patients not taking anticoagulants. Hydration and electrolyte balance should be in a satisfactory state, and the patient must be able to lie prone for a reasonable length of time (obviously those who have undergone surgery in the past week or so will not be able to maintain this position).

If the patient has had a CT scan for the diagnosis of the tumor, it is important to visualize the site and size of the tumor in relation to its surrounding structures.

If the patient has had a previous x-ray of the lumbar spine, it is important to note anatomical variations of T12 rib, which is occasionally absent; at first sight, the patient may appear to have six lumbar vertebrae, thus making it difficult to visualize which is L1.

Technique (4–6). The patient is placed in a prone position on a table, upon which a padded x-ray cassette box has already been placed, so that x-rays, when taken, will embrace the area involving the last ribs to the sacrum (7). A pillow is placed under the abdomen to cause flexion of the lumbar spine. An intravenous drip is started using 1000 ml Ringer's Lactate and a sphygmomanometer cuff is placed over an upper arm and the blood pressure noted. With a marking pencil an *X* is made over the spine to T12, counting downward from C7, and cross-checking by counting upward from the intercristal diameter which usually passes between L4 and L5. Another *X* is made at the level of the last rib, four fingers (7.5 cm) from the lumbar spine on the side of the worst pain (or left side if the pain is midline) (Fig. 1). A few days later, if there is persistence of pain and for contralateral pain, the contralateral side may be blocked.

Under sterile conditions through a skin wheal with local anesthetic a 6-inch needle, 18 gauge, is passed through the *X* four fingers from the midline in a direction toward the spine of T12, which is at the level of the body of the first lumbar vertebra, at an angle of about 45°. If bone is hit about 1½ inches from the skin, it is probably transverse process, in which case the needle must be redirected, caudad or cephalad, until bone is felt about three to four inches from the skin. The needle is then withdrawn and "walked" over the anterolateral aspect, just bypassing bone and made to rest ½ inch beyond that point (Fig. 2).

Anterior-posterior and lateral x-rays are now taken to confirm that the tip of the needle is indeed at the level of L1 and anterolateral to it. Any deviation from that situation necessitates repeating the procedure, and re-x-raying for position (Figs. 3, 4).

The celiac plexus (on the left side) is entwined around the aorta. If transmitted pulsations are present at the needle tip and aspiration for blood is negative, the position is considered satisfactory, provided x-ray confirms the needle position in front of L1 (preferably lower half of L1). If the aorta is entered, the needle should be withdrawn until blood can be no longer aspirated. Once the needle has been positioned, other confirmatory tests of needle placement should be performed in order to rule out improper placement of the needle tip. For instance, leakage of blood, urine, cerebrospinal fluid may sometimes be spontaneous, or gentle aspiration should be done.

A 2 cc test dose of anesthetic solution should be injected. This will provide confirmation of needle placement since paralysis rapidly follows if the

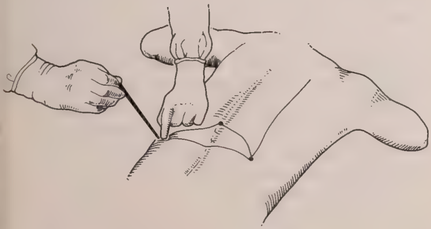
FIG. 1.

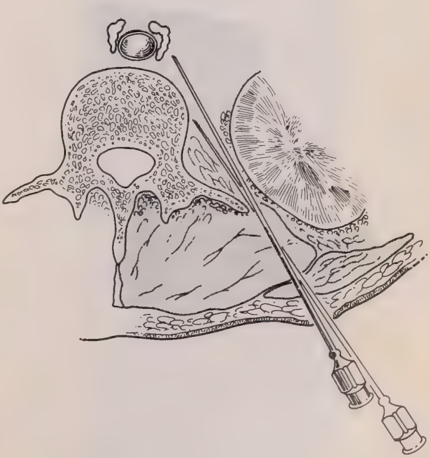
FIG. 2.

injection is subanachroid, while intravascular injection may be heralded by ringing in the ears and restlessness.

At this stage, 5 ml of 1% Lidocaine is injected. If pain relief follows and the blood pressure shows a slight fall, 20 ml absolute alcohol is slowly injected. After the first 5 ml or so is injected, pain will follow—usually severe, burning, like a "kick from a horse in the solar plexus." This is a good sign, and suggests that the celiac plexus has been entered. Some intravenous morphine or demerol can be given for the rest of the alcohol injection. Before removing the needle, a small amount of air or local anesthetic solution should be injected through the needle to avoid forming a track of neurolytic solution through the tissues or causing necrosis of peripheral nerves.

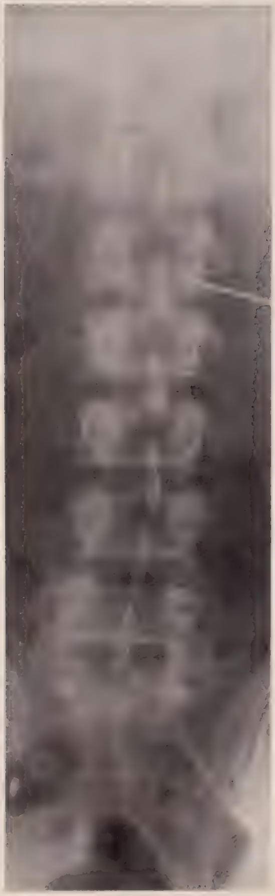

FIG. 3.

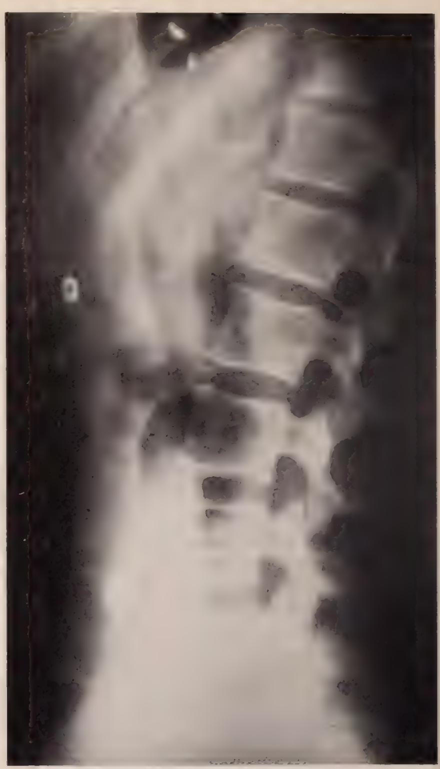

FIG. 4.

The patient should lie prone for 45 minutes following the celiac block. The patient may have pain in the back or epigastrium, or even the shoulders or anterior chest wall, for a short while; but this usually disappears. By the next morning, the pancreatic pain is usually gone.

Elsewhere other radiographic techniques have been described, using radiopaque catheters (7, 8), and Moore et al have presented a CAT scanning method for celiac plexus block (9).

Post-block Orders. Following celiac plexus block, a number of orders are clearly written on the chart, and discussed with the nurses involved.

1. Patient lies on stomach for 45 minutes, because alcohol is a light solution, and one does not want the solution to go wandering elsewhere in the retroperitoneal space.

2. Vital signs have to be taken every 15 minutes for the first two hours, and then four times daily.

3. Morphine or demerol is prescribed for severe pain.

4. Hydration must be attended to and adequate intravenous fluids and electrolytes must be given. If the patient is able to take sufficient fluids by mouth, the intravenous drip can be discontinued.

5. Postural hypotension is a real problem. Patients must be warned not to attempt to get out of bed without assistance, because they may faint. When getting out of bed they should use elastic stockings and an abdominal binder. They should not be discharged from hospital, even if pain-free, until compensatory reflexes have come into play (about 36 hours).

Results. In the past four years, we have performed celiac plexus blocks, mostly for pancreatic carcinoma, but also for chronic pancreatitis and some other chronic painful abdominal situations. Generally speaking, the results have been encouraging, especially for carcinoma (see Table). The patients themselves have frequently been surprised at the degree of pain relief, lasting from three months to two years. The series includes blocks done on the opposite side, and blocks done at a later date on the same patients. Only those patients who still had some pain following unilateral block received a block on the contralateral side a few days later. Occasionally, block on the one side also relieved pain on the opposite side.

Complications. Celiac plexus block is not an ambulatory procedure. Postural hypotension is the most serious of all the complications. The block having caused a sympathetic blockade, a large area of splanchnic blood vessels have dilated, causing a relative hypovolemic state. Celiac block must not be performed on patients who are dehydrated or in electrolytic imbalance. Prior to block, they should be rehydrated. Two (of 138) patients had fairly severe postural hypotension. One had a postblock cerebrovascular accident and was comatose for a few days; another, after fainting, was found to have hypotension and ST depressions which responded soon after volume was replaced and electrolyte balance returned.

TABLE

Results of Celiac Plexus Block
(138 procedures)

		Satisfactory Results	Complications (no.)
Indication	No.*	No. (%)	
Carcinoma of pancreas	80	68 (85%)	pleural effusions (2)
Chronic pancreatitis	50	35 (70%)	fairly severe postural hypotension (28)
Crohn's disease (post-surgery)	5	2 (40%)	dysesthesia at L_1 (2)
Retroperitoneal metastases	2	1 (50%)	shoulder-tip pain for a few days (5)
Pain following multiple laparotomies	1	0 (0%)	chest pain for a few days (8)
Total:	138	106 (78%)	

* Includes repeat and contralateral blocks.

Numbness or dysesthesia in the groin may occur if there has been leakage of alcohol on to the root of L1. This should not occur if x-ray control is available and the needle is well placed. Also, if the needle has been emptied by an injection of air or local anesthetic (about 2 ml), no track of alcohol will leak on to L1 or any other roots.

Frequently, there is still pain on the contralateral side, and even on the same side, after the block. This can usually be overcome by blocking the other side at a different session. There appear to be crossover fibers in the autonomic distribution from the celiac plexus. A block on one side may relieve pain on the contralateral side. We prefer not to block both sides at the same session, for fear of severe orthostatic hypotension.

According to Moore et al who used CT scanning, perforation of the kidney was a not uncommon complication (9).

Inadvertent penetration into aorta or inferior vena cava is not serious; the needle can be immediately withdrawn without causing any further bleeding (providing the prothrombin time, bleeding, and clotting times are normal). When withdrawing the needle, one has to be sure that the tip of the needle is not dissecting between the layers of the aorta.

Inadvertent subarachnoid injection has been reported. A case of paraplegia following celiac plexus block with phenol is described by Galizia and Lahiri(10), who postulate vascular ischemia as the possible cause for necrosis of the cord. The anterior radicular artery of Adamkewiez could become sclerosed with a neurolytic injection.

Occasionally, diarrhea develops following the block. This should be treated conservatively.

Shoulder-tip pain may last a few days, if diaphragm or branches of phrenic nerve have been involved. Most patients have some back pain due to the injection for a few days following it. Should the patient continue to have shoulder or pleuritic pain, a chest x-ray must be taken. Two patients in our series developed pleural effusions which resolved spontaneously. One had a high eosinophil count in the fluid. Neither effusion was sanguinous. They were probably reactive effusions following irritation of the diaphragm or diaphragmatic pleura.

Should there be vertebral or other bony metastases in the area, celiac block cannot be expected to alleviate pain. Radiculopathy, too, will not respond to celiac plexus block.

A patient who has been receiving large doses of narcotics may, despite pain relief, continue to complain of pain in order to continue to receive the pain medication and may resent discontinuance of narcotics.

Generally speaking, pain relief is remarkable, and most patients ask why this relief has been denied to them for so long. Relief has lasted from two months to two years. We have seen a 45-year-old travel agent relieved of pancreatic cancer pain for 18 months who then returned to the hospital for palliative bypass surgery and subsequently died—painlessly. We have seen a school teacher with pancreatitis whose surgery was cancelled because of pain relief from celiac block; the teacher returned 12 months later for repeat block, and again no surgery was done.

Fringe Benefits. Apart from pain relief, celiac plexus block has some fringe benefits: (a) Increased bowel motility, due to depression of sympathetic tone. More regular bowel movements follow, possibly also a result of decreased narcotics use. (b) Decreased use of narcotics. Families and friends now see an awake, alert, happier patient. (c) Less nausea and better appetite. But one patient, who had relief from pancreatitis for the first time in 25 years, told me that she lost her sense of hunger and satiation—this did not bother her, as she ate when the rest of the family ate.

Have we removed the warning signals for acute abdomen by blocking the celiac plexus? Nobody has documented that warning signals for an acute abdominal catastrophe have been removed. Vomiting, distension, constipation may all occur with an acute abdomen, even in patients who have had a celiac plexus block. Perhaps the physician will necessarily be more on guard in the presence of reduced pain. With this in view, the celiac plexus is clearly sacrificeable.

Summary. From an overview of our experiences with celiac plexus block, we conclude that it remains a worthwhile and valuable procedure for the treatment of retroperitoneal pain, especially carcinoma of the pancreas and pancreatitis (12). We disagree with those who have said that it usually produces unsatisfactory results in pancreatitis (13). We feel, with Jones and Gaugh (14), that despite the proximity of major vascular structures, and the short-lived problem of back pain from the needles and postural hypotension, celiac plexus block should not be denied to a patient with chronic pancreatic pain.

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Submitted for publication June 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Experimental Replacement of Canine Pericardium

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Abstract

Cardiac reoperation for congenital or acquired cardiac defects is often complicated by the presence of adhesions and loss of anatomic landmarks when the pericardium has been left open at initial operation. In this short-term study, we evaluated three materials for use as pericardial replacements: (a) segmented polyether polyurethane elastomer (Po), (b) silicone rubber (Si), and (c) processed bovine pericardium (Bo). Twenty-six dogs underwent replacement of portions of parietal pericardium with a total of 41 pieces of Po (17/41), Si (9/41), and Bo (15/41). Autopsy was performed an average of 50 days after implantation. With all three materials, adhesions to surrounding noncardiac structures (lung, etc.) were mild. Fibrous encapsulation of patch was frequently seen with Po (11/17); encapsulation was also noted with Si (3/9) and Bo (1/15). Adhesions between patch and heart were present in 2/17 Po, 3/9 Si, and 13/15 Bo; adhesions were judged severe in 7 specimens (2 Po, 2 Si, 3 Bo). A fibrous epicardial reaction underlying the materials, which obliterated the surface architecture, was seen with 17/17 Po, 9/9 Si, and 6/15 Bo. Pathologic examination revealed the reaction beneath Po and Si to be severe and on-going, with collagen deposition. The reaction under Bo was consistently less severe. In summary: Po was considered unsuitable as a pericardial replacement material because of frequent encapsulation and epicardial fibrosis. Si and Bo should facilitate reoperation by minimizing adhesions to both cardiac and noncardiac structures. However, the observed problems of encapsulation and particularly the fibrous epicardial reaction seen with Po and Si, which might impair identification of surface structure during reoperation, deserve further investigation in long-term models.

Reoperation for repair of congenital and acquired cardiac abnormalities is often complicated by the presence of adhesions and obliteration of anatomic landmarks between the heart and surrounding structures (1–2). While closure of the pericardium is desirable in order to minimize these changes, it is often not possible in the clinical situation. Therefore, various materials have been employed experimentally and clinically as replacements for native pericardium. These materials have included autologous fascia lata (3), glutaraldehyde-preserved porcine pericardium (4, 5), silicone rubber (6–10), and processed bovine pericardium (11).

The purpose of this paper is to report the results obtained in the canine model when native parietal pericardium was replaced with sheets of (a) segmented polyether polyurethane elastomer (Biomer, Ethicon Inc., Somerville, NJ), (b) silicone rubber (SciMed Pericardial Substitute, SciMed Life Systems Inc., Minneapolis, Minn.), and (c) processed bovine pericardium (Peri-guard, Genetics Laboratories Inc., St. Paul, Minn.).

Methods

Twenty-six adult mongrel dogs of either sex were used for this study. The dogs were anesthetized with pentobarbital sodium, 30 mg/kg IV (Fort Dodge Laboratories, Inc, Fort Dodge, Iowa), intubated, and ventilated mechanically (Air-Shields respirator, Hatboro PA). Using sterile

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technique, the lung was retracted and the pericardium exposed through a lateral thoractomy. In 16 animals, two circular portions of native pericardium approximately 5 cm in diameter were excised. In seven animals, only one defect in the pericardium was created. In the final three animals, a pericardial defect was created and a Dacron (E. I. DuPont de Nemours and Co) patch was sewn into the right ventricular outflow tract.

In all animals, the visceral pericardium was then abraded with a dry sponge; this maneuver was performed to increase the degree of adhesion formation under both the implanted materials and native parietal pericardium. The reaction under the natural pericardium could then be compared to that underlying the implants and thus could serve as a "control." The circular defects were closed with like portions of the three materials being tested.

The pericardial defect overlying the right ventricular outflow tract patch was closed using a large piece of either processed bovine pericardium (two animals) or silicone rubber. The implants were sutured in place using interrupted sutures. The lung was re-expanded and the chest closed. A chest tube was left in place for several hours after the operation. The animals were allowed to recover. They received penicillin G procaine suspension (Wyeth Laboratories, Philadelphia, PA), 600,000 units IM per day for seven days after the operation—a standard procedure in our animal facility.

As this was intended to be a short-term study, the animals were sacrificed by intravenous injection of Sleep-away (1 cc/2.5 kg; Fort Dodge Laboratories) an average of 50 ± 5 days ($\bar{x}$ ± SEM) after surgery. The region of pericardial replacement was inspected for pleural and pericardial adhesions. Photographs were taken. The specimens were then preserved in 10% formalin (neutral buffered) and refrigerated until microscopic pathologic analysis could be performed. Standard light microscopic procedures were employed in the study of the specimens. Although sections were taken both at the junction between the native pericardium and patch material and at areas well away from the suture line, only the areas away from the suture line were studied in detail. During specimen sectioning, the polyurethane elastomer and silicone rubber were removed from the paraffin blocks and, therefore, were not present in the sections.

Results

Twenty-six animals underwent surgery (Table I). Twenty-two animals were sacrificed 35 to 59 days following surgery. One animal was sacrificed 156 days after implantation. Three animals died at 6, 14, and 26 days after operation. The first died of wound separation and pneumothorax; no autopsy was performed. The second died from cardiac tamponade. The third animal died for unknown reasons but appeared healthy the day prior to death. One dog which was autopsied 52 days following implantation (polyurethane and silicone rubber) had gross pathologic evidence of pericarditis; the animal was asymptomatic when sacrificed.

A total of 41 specimens of implanted material from 25 hearts were available for study. No differences in the type or degree of reactions to the materials were appreciated between animals autopsied at four weeks and at eight weeks following surgery. The group was, therefore, evaluated as a whole.

Gross inspection at the time of autopsy revealed that in 20 animals, dry sponge abrasion (control procedure) was able to evoke a moderate degree of fibrous strands between the native visceral and parietal pericardium. These strands were easily dissected, and there was no significant loss of epicardial architecture. In two dogs, no adhesions formed, but, in three others, there were severe adhesions with loss of planes of dissection and surface architecture.

There were always adhesions at the pericardial suture sites. Pleural-to-patch material adhesions were frequently present, but all were minor; dissection of the lung from the pericardial replacement substances was readily accomplished. Table II summarizes the gross pathologic changes seen under the implanted materials. The polyurethane elastomer was associated with fibrous encapsulation of the patch in 11 of 17 specimens (Fig. 1).

TABLE I
Distribution of Implanted Materials

Replacement Material	No. of dogs	Deaths
Po + Bo	8	
Si + Bo	5	
Po + Si	3	1*
Po	7	2†
Bo + Dacron patch RVOT	2	
Si + Dacron patch RVOT	1	
	26	

Po: polyurethane elastomer; Si: silicone rubber; Bo: processed bovine pericardium; RVOT: right ventricular outflow tract.

* Cardiac tamponade 14 days postoperatively.

† One died of pneumothorax several days postoperatively; not autopsied. The other died of unknown causes 26 days postoperatively.

TABLE II
Gross Pathologic Results of Pericardial Replacement Experiments

	Polyurethane elastomer (n = 17)	Silicone rubber (n = 9)	Processed bovine pericardium (n = 15)
Encapsulation	11/17	3/9	1/15
With fluid accumulation	9	3	0
Without fluid accumulation	2	0	1
Pericardial adhesions*	2/17	3/9	13/15
Mild	0	1	10
Severe	2	2	3
Loss of epicardial architecture	17/17	9/9	6/15

* Judged at nonsuture sites.

Although the patch was not adherent within the capsule, the material was totally encircled and retracted upon itself. In nine instances, fluid had accumulated within the capsule. The fluid appeared purulent in four instances and serous in five. The purulent fluid was gram-stain positive for polymorphonuclear leukocytes but negative for bacterial organisms. Bacterial cultures were not obtained. The polyurethane elastomer resulted in a severe reaction on the underlying sur-

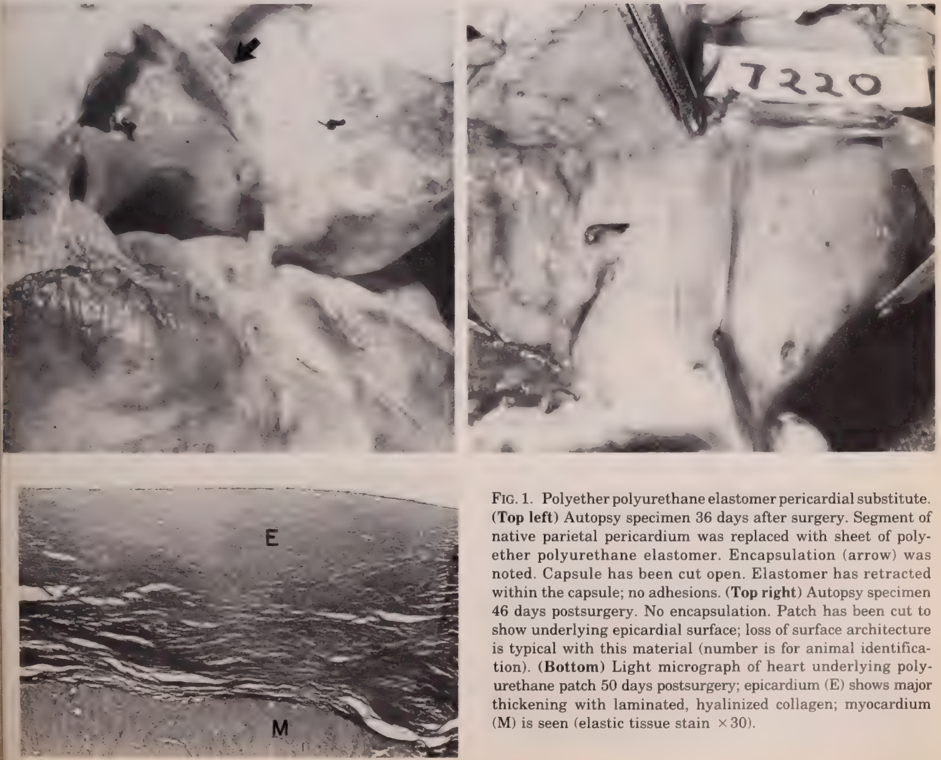

FIG. 1. Polyether polyurethane elastomer pericardial substitute. **(Top left)** Autopsy specimen 36 days after surgery. Segment of native parietal pericardium was replaced with sheet of polyether polyurethane elastomer. Encapsulation (arrow) was noted. Capsule has been cut open. Elastomer has retracted within the capsule; no adhesions. **(Top right)** Autopsy specimen 46 days postsurgery. No encapsulation. Patch has been cut to show underlying epicardial surface; loss of surface architecture is typical with this material (number is for animal identification). **(Bottom)** Light micrograph of heart underlying polyurethane patch 50 days postsurgery; epicardium (E) shows major thickening with laminated, hyalinized collagen; myocardium (M) is seen (elastic tissue stain ×30).

face of the heart in all specimens (17/17) (Fig. 1). This reaction was manifest as a white fibrous thickening of the epicardium with obliteration of surface cardiac architecture. Fibrous adhesions between the capsule and the epicardium were noted in two animals.

Three silicone rubber patches (3/9) were encapsulated, all with fluid accumulation in the manner described for the polyurethane elastomer. In one specimen, the fluid was purulent. The second encapsulation occurred in the animal which died of cardiac tamponade 14 days after surgery (Table I). The third encapsulation occurred in the animal with a silicone implant covering a Dacron right ventricular outflow tract patch. The patch was found to be encapsulated and retracted so that it no longer covered the Dacron material. Silicone rubber implants were also associated with a white fibrous epicardial reaction in all nine specimens (Fig. 2). Adhesions between the silicone and the visceral pericardium occurred in three specimens.

The processed bovine pericardium was noted to be encapsulated in one instance; the patch within the capsule had been partially digested. Loss of epicardial architecture occurred in six of 15 instances (Fig. 3). As with the other two materials, the white fibrous tissue reaction on the epicardial surface was believed to have the potential to impede identification of surface structures during reoperation. In 10/15 processed bovine pericardium specimens, there were mild adhesions, and in 3/15, there were severe pericardial adhesions. There were significantly more adhesions than with the other materials. The mild adhesions were loose, thin strands which were readily separated. The severe adhesions were believed to be of a degree which could interfere with dissection at the time of reoperation.

Microscopic examination of the specimens revealed the following. A well-defined capsule seemed to surround both the polyurethane and silicone materials. In some cases, the encapsulation resulted in retraction of the graft as well as fluid accumulation. For both the polyurethane elastomer (Fig. 1) and the silicone rubber (Fig. 2), there was evidence of ongoing deposition of collagen fibers which resulted in marked thickening of the visceral pericardium and replacement of the fatty epicardium. The thick, fibrous epicardium obliterated the heart. Although this was not evident clinically in these animals, the reaction was felt to be one which could lead to stricture.

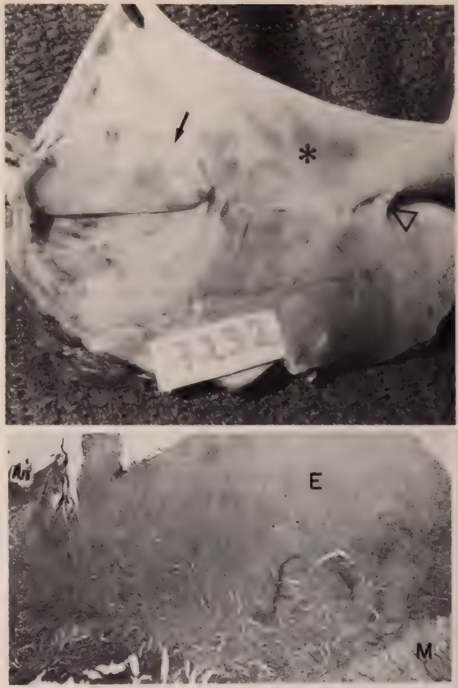

FIG. 2. Silicone rubber pericardial substitute. **(Top)** Autopsy specimen 52 days postsurgery. Circular silicone rubber patch (arrow) is being lifted with parietal pericardium (star) to demonstrate underlying surface cardiac architecture; severe loss of surface anatomy under patch, mild pericardial adhesions under native parietal pericardium (arrowhead). **(Bottom)** Light micrograph of heart underlying silicone rubber patch 35 days postsurgery; epicardium (E) is thickened by dense collagen; fibrin on the surface is undergoing organization. Myocardium (M) is seen (elastic tissue stain ×15).

The processed bovine pericardium (Fig. 3) was slightly adherent to the host tissue on the chest wall; however, the material was not invaded by host tissue. Fibrous deposition in the epicardium seemed mild. Fatty epicardium was evident, and the cardiac architecture was not severely disturbed in most specimens. There was no suggestion that this reaction would cause stricture although these experiments were, by design, short-term. No immune response was observed for any of the three materials used.

Discussion

The desired qualities for a pericardial substitute are as follows: (a) inhibits adhesion formation between extracardiac structures (sternum, pleura) and the heart, (b) is free of pericardial

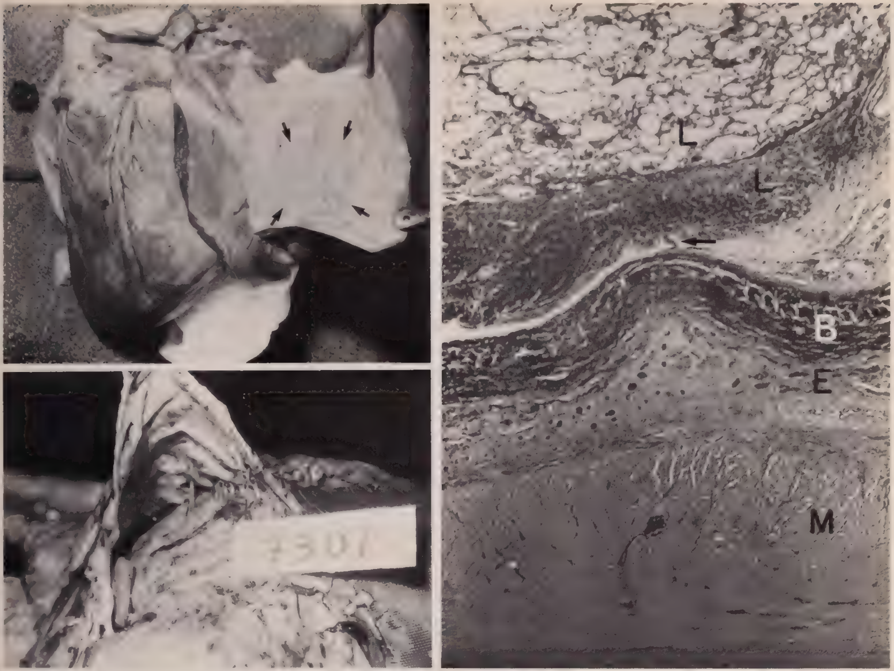

FIG. 3. Processed bovine-pericardium pericardial substitute. **(Top left)** Autopsy specimen 36 days postsurgery. Parietal pericardium has been lifted off cardiac surface. Pericardial replacement material (arrows) is intact. There were mild pericardial adhesions and minimal loss of epicardial architecture. **(Bottom left)** Autopsy specimen 43 days postsurgery. Multiple delicate adhesions beneath bovine material; severe obliteration of surface cardiac landmarks, the most severe surface reaction seen with this material. Silicone rubber implant is in place to right of bovine. **(Right)** Light micrograph 43 days after surgery. Section from representative specimen of implanted bovine pericardium with underlying heart. Epicardium (E), adjacent to bovine pericardium (B), shows slight thickening with vascular connective tissue. Delicate adhesions (arrow) bind lung (L) to outer aspect of bovine material. Hemorrhage in adhesions between bovine pericardium and lung. Myocardium (M). (Elastic tissue stain ×30.)

adhesions, (c) does not cause epicardial reaction with attendant loss of surface cardiac landmarks, (d) is biologically inert, and (e) is easy to implant and does not increase the possibility of infection or tamponade.

The present study was performed to ascertain whether the three materials tested displayed such favorable qualities in a short-term, canine model.

Segmented polyether polyurethane elastomer is a substance of favorable strength and flex life and appears to be biologically inert and relatively nonthrombogenic (12). Its experimental applications have included use as vascular grafts (13, 14), as a component in a left ventricular assist system (15), and as a chronic epicardial surface electrode (P. Danilo, Jr, unpublished). Because of its favorable properties, the elastomer was fashioned into sheets (P. Danilo, Jr, unpublished) and employed as a pericardial substitute.

This study suggests that while the substance as we prepared it was biologically inert, it was not suitable as a pericardial replacement material. It was noted to be contracted and encapsulated, often with purulent fluid accumulation. The fluid was thought to arise either from a foreign body reaction or from infection. Arguing against an infectious process were the facts that the animals were clinically well, had received antibiotics postoperatively, and evidenced no bacterial organisms on gram stain of the fluid. These features hardly exclude infection as an etiology, however.

Future studies will have to explore the nature of this fluid accumulation in more detail. The loss of epicardial architecture associated with a severe reaction in the visceral pericardium and epicardium defeated one of the main purposes of the intended use of the elastomer. The reasons for this marked foreign-body reaction, which develops rather promptly, are unclear.

Silicone rubber has now been clinically used as a pericardial replacement substance by Laks et al (9). They implanted the substance in 102 patients, both adults and children. No infections occurred. Reoperation was performed on seven patients. The silicone rubber resulted in a tissue-free space around the patch which facilitated the safe opening of the sternum. Laks et al note, however, that "the underlying cardiac surface was covered by a smooth dense white layer of connective tissue, which was separated from the myocardium by the epicardial fat." The present study is in agreement with this observation; epicardial surface obliteration was seen in all specimens. As with the polyurethane substance, patch retraction and encapsulation as well as pericardial adhesions were also noted.

Pathologic evaluation demonstrated replacement of the fatty epicardium with thick, fibrous tissue. Surface structure was obscured, and there was a suggestion of ongoing collagen fiber deposition. The causes of this severe reaction are not presently known. One animal died of cardiac tamponade; another had evidence of pericarditis. Both had polyether polyurethane elastomer and silicone rubber implants. While it cannot be ascertained from this study whether the materials were causative of these conditions, concerns over tamponade and pericarditis have been raised in the clinical study of Laks et al (9).

Results using processed bovine pericardium as pericardial replacement material have been reported by Meus and others (11), who suggested that bovine pericardium was a replacement material with favorable properties. The present short-term study suggests that the bovine material is subject to problems similar to those occurring with both polyether polyurethane elastomer and silicone rubber. Bovine pericardial-to-canine visceral pericardium adhesions occurred significantly more frequently with this material. However, the adhesions were usually minimal. Adhesions to the chest wall were also minimal.

The white fibrous deposition in the epicardium was present in six of 15 specimens. Microscopically, the reaction to the bovine pericardium was less severe and less dynamic than to the two other materials. In the other nine specimens, the surface architecture was preserved. In two animals in which the bovine pericardium was placed over a Dacron right ventricular outflow patch, surface adhesions were minimal, and the planes of dissection were well-maintained.

Summary

The results of this short-term study of pericardial replacement with polyurethane elastomer, silicone rubber, and processed bovine pericardium suggest the following conclusions. Segmented polyether polyurethane elastomer as constituted for this study was unsuitable as a pericardial substitute. Silicone rubber and processed bovine pericardium should facilitate cardiac reoperation in respect to opening the sternum safely and dissecting the lung away from the heart, if necessary. Silicone rubber frequently causes a severe fibrous reaction in the epicardium which will obliterate surface architecture and hinder reoperation. Cardiac tamponade may also occur with this material (9).

Additional concerns of encapsulation and retraction of the patch have been shown in the present study. Processed bovine pericardium seems to be more effective than silicone rubber in the maintenance of surface cardiac anatomy. The reaction is less frequent and more static than with the silicone material. Also, the adhesions between the bovine material and the visceral pericardium are usually mild. However, encapsulation may occur.

When either the bovine or silicone material is used, large pieces covering the entire anterior pericardium should be implanted to keep the adhesions that form at the suture site away from the sternum. Adequate postoperative drainage should be employed to drain any accumulated fluid.

Further experimental work with both these materials is warranted to (a) evaluate long-term effects, (b) assess the need for antibiotics in the postoperative period, and (c) study the etiology of this "foreign body" reaction. Special consideration should be given to the question of cardiac constriction resulting from the epicardial reaction occurring under these materials. It is open to question at this point whether in long-term usage these materials will prove advantageous when compared with leaving the pericardium open.

Acknowledgments

We thank Dr. Jesse Edwards, United Hospitals, St Paul, Minnesota, for performing the pathologic evaluation, Mrs. Isabella Hewitt for secretarial assistance, and Mr. Ruben Rivera for postoperative care of the animals.

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Submitted for publication March 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Selective Gastrointestinal Circulatory Changes due to a Vasopressin Hormonogen in the Cat

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Abstract

The effect of an endogenously activated hormonogen of vasopressin, triglycyl lysine vasopressin, on gastrointestinal blood flow measured by labeled $^{86}RbCl$ was studied in 14 male cats. Following bolus injection of hormonogen, decreases were noted at 30 and 60 but not 120 minutes. Flows from proximal esophagus to rectum were diminished, except for non-statistically-significant increases in colonic and hepatic arterial blood flow. This study demonstrates changes caused by a vasopressin hormonogen on feline splanchnic blood flow.

Vasopressin (VP) has been employed in the management of variceal hemorrhage since "Surgical Pituitrin" was first introduced in 1956 (1). Its usage is limited by its effect on the myocardium (fall in cardiac output, coronary vasoconstriction which may lead to arrhythmias, and infarction) and coagulation parameters (increased plasminogen activation). Tachyphylaxis has been reported.

Triglycyl lysine vasopressin (Glypressin, tGLVP) is a VP hormonogen. The intact molecule has no action on smooth muscle. Cleavage of lysine fragments, in vivo, results in a slow release of active hormone. Therapeutic doses do not affect the myocardium or alter hemostatic mechanisms. Doses of tGLVP equipotent to a therapeutic dose of VP have been shown to constrict smooth muscle at 10 hours (2). Recently, prospective clinical studies comparing tGLVP to VP have suggested that tGLVP, "because of its efficacy, lack of side effects, and ease of administration," may be beneficial in the management of bleeding esophageal varices (3). This report demonstrates in detail the sites of action of this hormonogen in the feline splanchnic circulation.

Methods. Fourteen adult male cats weighing 2 to 2½ kg were deprived of food for 24 hours and water for two to six hours. Anesthesia was induced with 33 mg/kg pentobarbital intraperitoneally, supplemented when ear or limb reflexes were elicited with 10 mg pentobarbital intravenously. The right carotid artery and external jugular vein were cannulated with No. 22 Angiocath. Using a polygraph recorder, baseline blood pressure and heart rate measurements were taken. Animals were then given a bolus injection, in less than 20 seconds, of either 0.5 ml normal saline (control group) or 10 $\mu g/kg$ tGLVP in 0.5 ml normal saline (experimental group). (tGLVP was provided by Ferring Pharmaceuticals, Malmo, Sweden). Blood pressure and pulse measurements were repeated 5 minutes prior to sacrifice, which was at 30, 60, or 120 minutes following drug administration.

Blood flow was determined using the methods of Sapirstein (4) with the modification of Delaney (5). Briefly, $^{86}RbCl$ 20 $\mu Ci/kg$ was given as a rapid intravenous bolus. Animals were sacrificed 1 minute later with 1 ml 3M KCl intravenously. Systolic cardiac arrest occurred in three to five seconds. ^{86}Rb is analogous to radioactive potassium. It diffuses across cell membrane on the first pass. Providing circulation is arrested 1 minute

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Presented in part at Ferring Symposium on Brain and Pituitary Peptides, March 1979, and at the American College of Gastroenterology 44th Annual Meeting, 1979.

TABLE

Changes in Gastrointestinal Tract Blood Flow

(% cardiac output measured by ^{86}RbCl)

	Controls* (n = 6)	tGLVP* 10 µg/kg IV (n = 6)	% Change	Significance Student *t*
Foregut				
Proximal esophagus	0.15 ± 0.06	0.10 ± 0.01	−33	
SM	0.08 ± 0.03	0.07 ± 0.009	−12.5	
Mucosa	0.07 ± 0.03	0.03 ± 0.004	−57	
Distal esophagus	0.24 ± 0.01	0.12 ± 0.01	−50	
SM	0.13 ± 0.02	0.07 ± 0.004	−46	
Mucosa	0.10 ± 0.01	0.05 ± 0.009	−50	
Total Esophagus	0.37 ± 0.08	0.22 ± 0.02	−40	NS
Cardia of stomach	1.86 ± 0.21	0.79 ± 0.19	−57	
SM + serosa	0.38 ± 0.04	0.16 ± 0.03	−58	
Mucosa	1.48 ± 0.20	0.63 ± 0.16	−57	
Antrum of stomach	0.41 ± 0.05	0.21 ± 0.04	−49	
SM + serosa	0.16 ± 0.02	0.08 ± 0.01	−50	
Mucosa	0.25 ± 0.04	0.13 ± 0.03	−48	
Total Stomach	2.25 ± 0.19	1.00 ± 0.17	−55	<0.005
Mid Gut				
Duodenum	1.80 ± 0.37	1.21 ± 0.04	−32	
SM	0.40 ± 0.06	0.33 ± 0.04	−18	
Mucosa	1.40 ± 0.33	0.88 ± 0.07	−37	
Jejunum	8.54 ± 0.49	3.92 ± 0.40	−55	
SM + serosa	2.14 ± 0.21	1.11 ± 0.14	−48	
Mucosa	6.40 ± 0.34	2.81 ± 0.34	−57	
Ileum	5.1 ± 0.79	3.54 ± 0.31	−31	
SM + serosa	1.46 ± 0.29	1.16 ± 0.17	−21	
Mucosa	3.70 ± 0.59	2.38 ± 0.27	−36	
Total small gut	15.49 ± 0.38	8.68 ± 0.52	−44	<0.001
Hind Gut				
Colon	2.09 ± 0.27	2.58 ± 0.72	+19	
SM + serosa	0.56 ± 0.12	0.57 ± 0.16	+02	
Mucosa	1.70 ± 0.27	2.01 ± 0.58	+15.5	
Rectum	1.29 ± 0.24	0.40 ± 0.07	−69	
SM	0.28 ± 0.10	0.08 ± 0.02	−71	
Mucosa	1.00 ± 0.20	0.31 ± 0.06	−69	
Total large gut	3.36 ± 0.33	2.98 ± 0.69	−11	NS
Pancreas	0.93 ± 0.14	0.38 ± 0.07	−59	
Spleen	1.22 ± 0.22	0.95 ± 0.24	−22	
Total portal	23.2	12.6	−46	<0.001
Liver (arterial)	11.69 ± 0.57	15.26 ± 1.50	+30	NS

SM = smooth muscle

* Combined 30-min and 60-min totals.

following injection, the radioactive content of each organ gives an accurate estimate of blood flow through all organs except lung and brain (4).

The entire gut, from proximal esophagus to distal rectum, was removed, opened, and gently cleansed of any content with dry gauze. Each specimen was divided, using sharp and blunt dissection, into two sections, (a) mucosa with the submucosa, and (b) muscle with the serosa. The total organ and its aliquots to be counted were weighed using a Mettler balance.

The esophagus was bisected and aliquots taken from the midpoint of each section. The stomach was divided into corpus and antrum by the gross appearance of the loss of rugosity, and an aliquot was removed. The aliquot from the duodenum was removed from its midpoint. The small bowel was bisected and the aliquot of each portion was removed from the specimen midpoint for ileum and jejunum. The large bowel was divided into colon proper and rectum, the landmark being the inferior mesenteric artery. The liver was removed in toto, weighed, and aliquots taken from left and right halves. Specimens were placed in the lower 2.5 cm of 16 × 100 glass test tubes and measured at 1.10 MEv in an LKB Ultra Gamma II counter. Calculations were made by the standard formula (2).

Results. There was no significant change in blood pressure or heart rate with tGLVP (see Table). At 30 and 60 minutes following a bolus injection of tGLVP, a marked decrease in gastrointestinal blood flow was observed; it was no longer evident at 120 minutes. Since there were no significant differences, values in the table are the combined 30-minute and 60-minute studies.

There appear to be selective decreases within the gastrointestinal circulation. A significant reduction of pancreatic blood flow was found. Decreases began in the esophagus but were most pronounced in fore- and mid-gut. Whereas the rectum showed a decrease in blood flow, the colon, unique in the GI tract, showed a nonsignificant increase. There was a 40% decrease in summated portal blood flow. Hepatic arterial flow showed a nonsignificant 30% increase.

Discussion. Potentially the most significant finding of this study is the hepatic arterial blood flow (HAF), which shows a 30% nonsignificant increase. These data concur with Blei et al (6) who found, using electromagnetic flow meters, an increase in HAF with tGLVP which was not found with vasopressin. The hemodynamics of hepatic blood flow are complex (3, 7, 8) and have recently been comprehensively reviewed (9, 10). A reciprocal relationship exists between hepatic arterial and portal venous flow rates. Indeed, in cirrhotic patients, the failure of the hepatic artery to exhibit an adequate increase in flow after portosystemic decompression has been suggested as a prognostic indicator (11). Whether this increase in HAF is of clinical relevance requires further study.

The changes in intestinal blood flow found following tGLVP agree with the decrease in portal circulation which has been observed with vasopressin (5, 12–14). We have demonstrated specific decreases throughout the GI tract. These changes begin in the esophagus and involve the entire stomach, small bowel, and rectum.

The colon, however, responds in a different fashion. There are significant increases in both layers, more pronounced in the mucosa (see table). This may be related to the marker, ^{86}Rb, being analogous to radioactive potassium, since the colon is a potassium excretor. In addition, mechanical stimulation due to stool in the colon may have interfered with the colonic response to tGLVP.

The decrease in pancreatic flow correlates well with demonstrated decreases in pancreatic blood flow with vasopressin (13) and inhibition in exocrine pancreatic secretion with vasopressin (15) and tGLVP (16).

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Submitted for publication June 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Keratinizing and Calcifying Odontogenic Cyst of the Mandible: Literature Review and A Case Report

ALAN M. SCHWIMMER, D.D.S., CHARLES E. BARR, D.D.S., AND STEWART J. GRAUER, D.D.S.

Abstract

A thirteen-year-old boy had swelling of the left mandible. Clinical and radiographic examinations revealed a large radiolucent area with expansion at the angle of the left mandible and ascending left ramus. It was necessary that the correct diagnosis be established prior to definitive treatment in order to reduce postsurgical morbidity. A diagnosis of keratinizing and calcifying odontogenic cyst (KCOC) was made from the biopsy. The KCOC is a relatively rare oral analogue of the dermal pilomatrixoma. At times it is misdiagnosed as an ameloblastoma, with subsequent excessive surgical intervention. This paper provides an in-depth review of the literature, describes the histologic characteristics of the lesion, and finally details the successful management of the patient.

The keratinizing and calcifying odontogenic cyst (KCOC) is a rare odontogenic lesion probably first described in 1932 by Rywkind (1). In 1946, Thoma and Goldman (2) described a similar lesion that they referred to as a strange variant of an ameloblastoma. In 1962 Gorlin et al (3) reported 11 cases of what they believed was an oral analogue of the cutaneous epithelioma of Malherbe, or pilomatrixoma. By 1968, a total of 30 cases of this clinical entity had been reported.

In 1975 Freedman and co-workers (4) reviewed a total of 64 cases, to which they added six more. A review of the literature subsequent to their report noted 13 additional cases—a total of 83 reported cases (5–7). The report here describes an extensive lesion of the left mandible and compares the histology of the KCOC to that of the pilomatrixoma.

Although the KCOC has been reported as occurring in a wide age range (8), most authors have placed the greatest frequency of occurrence prior to the fourth decade (5, 6, 8). The majority of lesions occurred in the toothbearing areas of the jaws. The review of Freedman et al (4) demonstrated an equal distribution of the lesion between the maxilla and the mandible. However, Petri and Stump (6) reported 70% of the lesions as occurring in the mandible. Although the KCOC may occur centrally or peripherally (9), both Altini (5) and Petri and Stump (6) reported 75% of the cases as occurring centrally in bone.

The radiographic and clinical presentation of the KCOC is generally nonspecific and not diagnostic. Most often its clinical pattern is benign and cystic, being slow-growing and expansile (5). Radiographically, the lesion may be unilocular or multilocular, and usually it has a well-demarcated peripheral border (4). Some authors (4–6, 10, 11) have reported the appearance of small irregular calcifications within the body of the lesion.

Pilomatrixoma. Histologically the KCOC is distinct and most interesting. Since Gorlin (3) described the lesion as being the oral equivalent of the epithelioma of Malherbe, a description of that lesion is instructive. Usually the pilomatrixoma or calcifying epithelioma of Malherbe (Fig. 1) appears as a firm, deep-seated nodule of the face or upper extremities and is frequently found in children and young adults (12). The tumor is located in the dermis, extending into subcutaneous tissue. It is composed of two types of epithelial cells, basophilic and shadow cells. The deeply

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staining basophilic cells show a gradual loss of their nuclei and finally appear as shadow or ghost cells containing an eosinophilic cytoplasm. The cytoplasm is strongly SH-positive, indicating accumulated keratin filaments. Electron microscopy confirms the evolution of the basophilic epithelial cells into more mature cells containing keratin filaments. The maturer cells in the lesion undergo gradual nuclear degeneration with eventual disappearance of the nucleus. The evolution of basophilic epithelial cells into mature eosinophilic ghost cells is not unique to the pilomatrixoma, and in fact bears a striking resemblance to the transitional process that occurs in the KCOC (13).

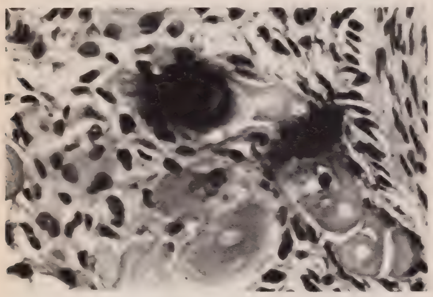

FIG. 1. Pilomatrixoma. Hyperchromatic epithelial cells surrounding keratinized "ghost cells" and calcified droplets (hematoxylin and eosin ×500).

KCOC. The KCOC is generally described as a multicystic lesion in which the cysts are lined with an irregular layer of epithelium of varying thickness. In some of these mural areas, the epithelium may bear a striking resemblance to ameloblastic epithelium, having a distinct columnar basal cell layer associated with a stellate reticulumlike formation (4, 10, 11). The nuclei of these basalar cells are polarized away from the basement membrane in a manner similar to that of enamel epithelium (3). This ameloblastic resemblance can be quite striking, and Bhaskar has suggested the term keratinizing ameloblastoma for this lesion (14). In a series of nine cases Altini and Farman (5) noted mural areas which they felt had a striking resemblance to an ameloblastoma.

A major feature which identifies the KCOC with the pilomatrixoma is the presence of the so-called "ghost cells." These cells have a granular, markedly eosinophilic cytoplasm and lack nuclei. The content of the ghost cells is believed to represent an aberrant form of keratin (4). Electron microscopic studies have demonstrated that the keratin found within these cells does not have the pattern of normal keratin, but rather represents a degenerative process. Cells containing keratin of a similar nature are found in a number of other pathologic states within the oral cavity, including simple odontogenic cysts, ameloblastic fibro-odontomas, keratinizing squamous cell carcinomas, and complex and compound odontomas (11, 15).

Gorlin's (3) original description of the histogenesis of this lesion is still considered classic. He and his associates stated that initially a cyst was formed which had a thin epithelial lining with a prominent basal cell layer. As the cyst developed, the basal cell layer became columnar, the nuclei polarizing away from the basement membrane. At that point, the epithelial cells take on the appearance of enamel epithelium. This phenomenon of epithelial cell transformation into enamel epithelium is not demonstrated in the pilomatrixoma. Since the epithelium in the KCOC is odontogenic, the prominent basal cells have the capacity to transform into cells containing the dystrophic keratin. This capability has been described by Freedman (4). He observed that the epithelial cells responsible for amelogenesis can produce keratin and suggested that the cells of origin of the KCOC may be the well-differentiated ameloblast and that the transformation of enamel epithelium into keratin containing "ghost cells" may be the normal evolution of ameloblasts in a connective tissue stroma devoid of calcified dentin. Thus ameloblasts are capable of proliferating and producing an enamel matrix which resembles keratin. However, due to the lack of calcified dentin, the enamel matrix does not mineralize.

The fact that the ameloblasts of the KCOC are well differentiated may help to explain the noninvasive nature of this lesion. The evolution of ghost cells is a critical step in the overall histogenesis of this lesion. Initially, the cells in the upper portion of the epithelial layer transform into ghost cells. As the epithelium thins out, the basal layer begins to participate in this transformation. As this occurs, the epithelial-connective tissue interface becomes indistinct. When connective tissue comes into contact with the ghost cells, the dystrophic keratin within the cells initiates a foreign body reaction. Masses of ghost cells fuse, and calcium salts are deposited within the keratin; calcified foci then develop.

Classification as a Cyst. Perhaps the greatest controversy concerning the KCOC centers around its classification as a cyst. The presence of enamel epithelium and an associated stellate reticulum as a mural phenomenon in the lesion have caused some to consider the lesion a variant of ameloblastoma (10). In 1971, the WHO Committee on the Histological Typing of Odontogenic Tumors, Jaw Cysts and Allied Lesions defined the KCOC as a nonneoplastic cystic lesion (6). There is no doubt that in some areas of the cyst wall the lining bears a striking resemblance to ameloblastic epithelium. In the largest series of cases reviewed, 88.5% of the lesions were reported as cystic, and 11.5% were reported as solid neoplasms (4). Seeliger and Reynke (7) described the KCOC as a lesion of highly differentiated ameloblasts with a prominent cystic component.

Praetorius and associates (11), in a review of 16 cases of calcifying odontogenic cysts, commented on the wide variation in appearance of the lesion, and the existence of a neoplastic variant. They proposed the existence of two distinct entities, a cystic form and a neoplastic form. For the neoplastic form the term "dentinogenic ghost cell tumor" was suggested.

The cystic variant was further subdivided into three groups. Type 1A was described as the simple unicystic variant. The lesion contained a sparse amount of dentinoid with a thin epithelial lining only two or three cells thick. The appearance of ghost cells and stellate reticulum was focal. Type 1B was identified as odontome-producing. This lesion contained multiple odontome-like formations projecting from the periphery of the lesion toward the lumen of the cyst. Type 1C was classified as the ameloblastomatous proliferating type. This was the most uncommon variant. It contained ameloblastomalike proliferations in the connective tissue of the fibrous capsule as well as in the lumen.

Biologically, the type 1 variant of the KCOC behaves as a cyst (11). It is slow-growing, does not cause dysesthesia, and does not demonstrate an aggressive pattern of bone destruction. Only one case of recurrence (4) has been reported, and that was in a patient in whom the lesion was a solid mass, the type described by Praetorius et al (11) as a "type 2 variant." In view of the continued ambiguity concerning the nature of the KCOC, the treatment of choice remains enucleation rather than decompression.

Case Report

A 13-year-old Hispanic boy was referred to the dental department at the Beth Israel Medical Center for evaluation of a large expansile mass of the left mandible. The patient stated that he had only been aware of the mass for three days.

On physical examination the patient was found to have marked asymmetry of the face. No sensory deficit was present. On palpation the mass was firm and nontender, and no associated lymphadenopathy was appreciated. Intraorally, marked expansion of the lateral cortex was present. The overlying mucosa was intact, and the medial cortex was compressible on palpation. No dysphagia was noted, and the remainder of the cranial nerve evaluation was within normal limits.

Radiographic examination (Fig. 2) showed a 4 cm × 10 cm unilocular radiolucency involving the entire ascending ramus of the left mandible

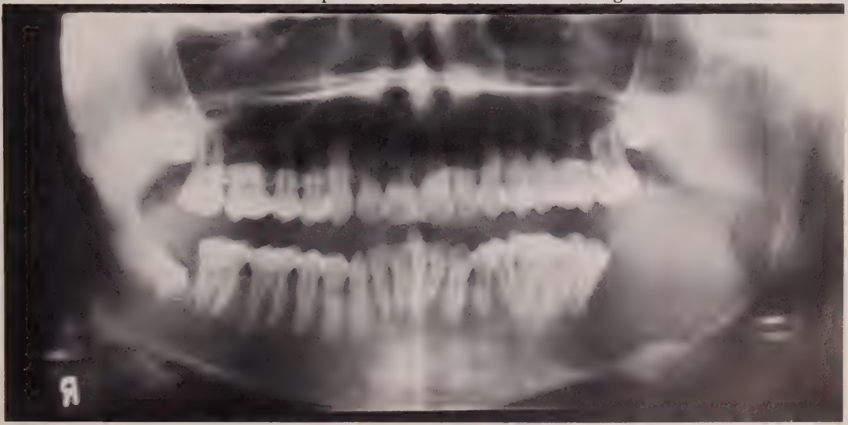

FIG. 2. Panoramic radiograph showing well-defined radiolucent lesion involving the ascending ramus of the left mandible, and extending up to the condylar neck.

and extending anteriorly to the first molar. Computerized axial tomography (Fig. 3) of the mandible confirmed the presence of a cystic, expansile lesion with an intact medial cortex and inferior border. Neither radiographic study showed any invasion of the condylar neck. The differential diagnosis included primordial cyst (keratocyst) and ameloblastoma. During that same visit, an incisional biopsy of the lesion was performed (Fig. 4). The specimen was described as follows:

> The section was composed of a portion of an epithelial lined cyst. It contained several layers of stratified squamous epithelium with a distinct basal layer of cuboidal to columnar type cells. At one point in the lining of the cyst was an irregular accumulation of large hyperchromatic epithelial cells in a follicular arrangement surrounding a stellate reticulumlike substance. Other hyperchromatic epithelial cells were loosely arranged in groups adjacent to a large number of pale-staining eosinophilic "ghost cells"—distinct, individually keratinzed epithelial cells. Droplets of calcified material were also noted among the epithelial cells adjacent to the ghost cells. In several ghost cells, melanin granules were also seen.

The diagnosis was consistent with a keratinizing and calcifying odontogenic cyst (Gorlin cyst).

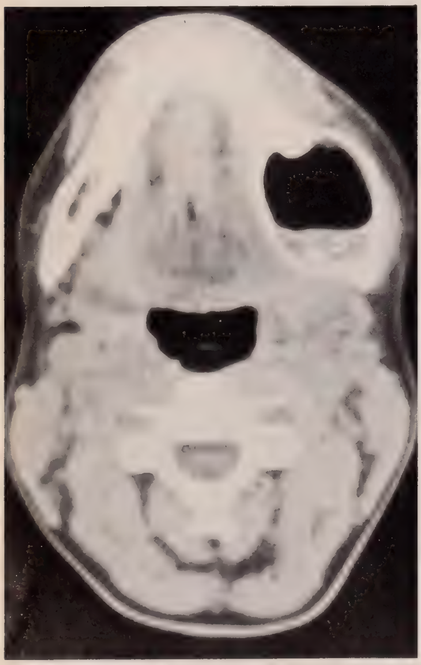

FIG. 3. Computerized tomogram showing mediolateral extent of the lesion and the presence of an intact medial cortex.

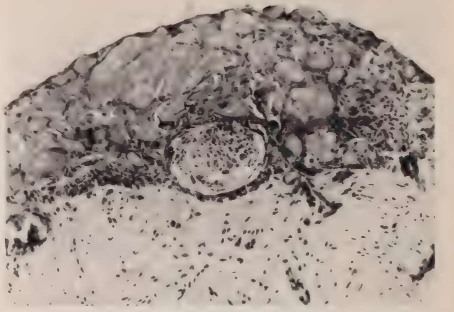

FIG. 4. Biopsy showing epithelial lined cyst with calcifications and keratinized epithelial ghost cells; consistent with KCOC (hematoxylin and eosin ×125).

The patient was admitted to the hospital for enucleation of the lesion, and autogenous bone grafting with primary closure. On admission, all laboratory tests and the chest radiograph were within normal limits. At surgery, the mass was readily enucleated. The lining of the cyst was found to be relatively thickened and the boney crypt was seen to be intact throughout its periphery. The cystic cavity was then packed with autogenous cancellous bone harvested from the right iliac crest, and the overlying mucosa was closed primarily. The patient's postoperative course was uneventful. There was no postoperative sensory deficit, and the patient was discharged on the fourth postoperative day to be followed as an out-patient.

The surgical specimen consisted of tissue that

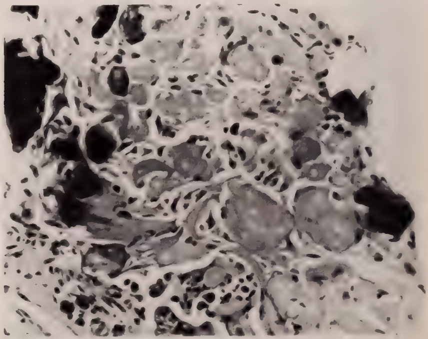

FIG. 5. Keratinizing and calcifying odontogenic cyst. Surgical specimen exhibiting essential elements of hyperchromatic epithelium, ghost cells, and droplets of osteodentin (hematoxylin and eosin ×245).

was lined by stratified squamous epithelium and which exhibited at numerous places strands or buds of ameloblastic-type epithelium which projected into the underlying loose, almost myxomatouslike connective tissue. At several areas along the periphery, accumulations of calcified material, appearing as osteodentin, were noted. Multiple nests of large hyperchromatic epithelial cells mixed with eosophilic keratinized epithelial ghost cells were seen. Numerous large and small droplets of osteodentin were also seen among the ghost cells. The surgical specimen confirmed the original biopsy diagnosis of keratinizing and calcifying odontogenic cyst (Fig. 5).

Discussion

Enucleation rather than decompression is the treatment of choice for this lesion. Lesions larger than 2 cm do not heal dependably without bone grafting (17). Achieving primary closure over such large defects is quite difficult, and the potential for dehiscence of the overlying mucoperiosteum is significant. Should this occur, the resulting defect would have to fill in by secondary intention. In a defect of this size, such a reparative process would be prolonged and incomplete and could easily result in a significant deformity of the ascending ramus.

Even with successful primary closure, it is known that hematomas which may form in such large defects organize from the periphery. Such peripheral organization can require up to two years for complete ossification, and even in juveniles, residual areas of fibrous connective tissue are likely to remain within the defect. The osteogenic capacity of a given area is directly proportional to its vascularity; the center of such a large defect is usually poorly vascularized, and therefore exhibits almost no osteogenic capacity (18).

It has been shown that autogenous cancellous bone is the most osteogenic of bone grafts (15). Such a graft contains competent mesenchymal cells, collagenous fibrils, intercellular substance, and apatite crystals. These constitute the materials which Urist and co-workers (19) have referred to as the inductive substrate. As is the case in any graft, initial vitality is maintained by diffusion and then by revascularization. In a cancellous graft, initial osteogenesis is carried out primarily by surviving osteoblasts, and secondarily by the inductive capacity of intercellular and cement substances (mucopolysaccharides) acting on the undifferentiated mesenchymal cells in the defect. The osteogenic and inductive phases complement one another, provided that the location of the graft bed is adequately perfused and the transplanted material is stable (18).

Large cystic cavities of the maxillofacial area are ideal host sites for osteogenic grafts. They offer good vascularization at the periphery, close contact with a wide surface of bone, and the absence of mechanical motion. Speissel has reported a series of 14 cases of cystic lesions of the mandible successfully grafted with cancellous bone (18).

The case described in this report represented an ideal situation for such treatment, which provided rapid resolution of the defect and mini-

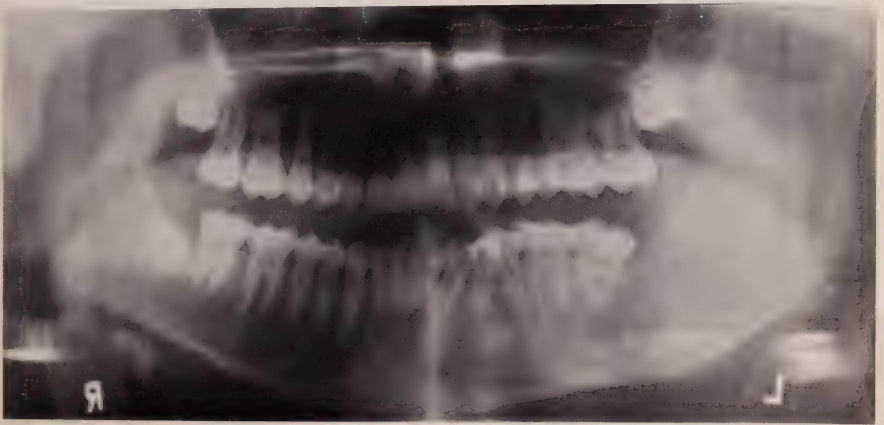

FIG. 6. Panoramic radiograph showing bone graft four months after placement.

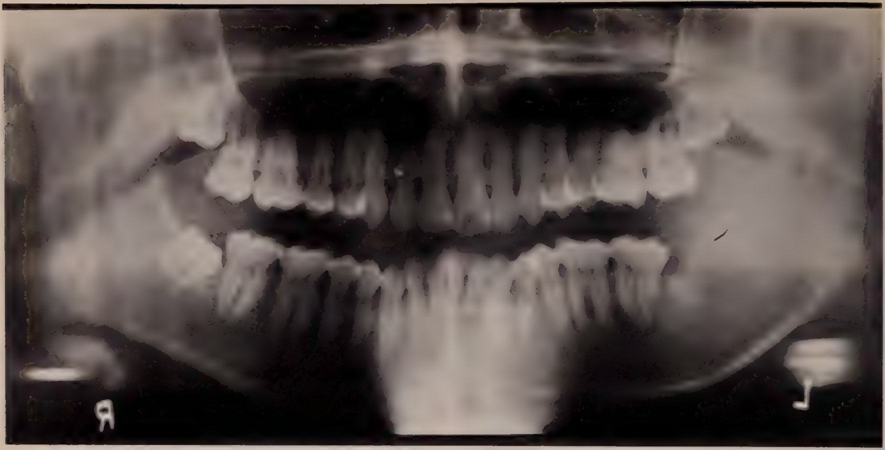

FIG. 7. Fourteen-month follow-up radiograph illustrating consolidation and maturation of cancellous bone graft.

mized the possibility of a residual deformity in an adolescent (Figs. 6, 7).

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Submitted for publication April 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Malignant Retroperitoneal Paraganglioma: Unusual Light and Electron Microscopic Findings

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Abstract

Several retroperitoneal paragangliomas have been described at the light and electron microscopic level; however, in the tumor reported here, the histologic presentation of the biopsy and autopsy specimen were unusual except for one small region in the latter that showed the typical zellballen pattern only after electron microscopy confirmed the nature of the tumor. At the ultrastructural level, the surgical specimen showed features of a paraganglioma, containing small dense-core granules, interdigitating cell processes, ring-shaped nucleoli, desmosome-like membrane plaques and a dark-light electron density distribution of plump and spindle cells with a connective tissue stroma forming a gland-like arrangement. Also unusual was the presence of large quantities of glycogen in the majority of cells. This finding suggests that some paragangliomas have the ability to synthesize and store glycogen. The diagnosis of retroperitoneal paraganglioma would not have been entertained without ultrastructural study of this tumor.

Although paragangliomas arise most often from the adrenal medulla, these tumors, composed of specialized neural crest cells, can also be found in association with the segmental or collateral autonomic ganglia throughout the body. The anatomical classification of the extraadrenal paraganglion system is usually subdivided into 3 groups: (a) branchiomeric and intravagal paraganglia; (b) visceral autonomic paraganglia; and (c) aorticosympathetic paraganglia.

One of the most unusual extraadrenal sites where paragangliomas can arise is the retroperitoneum. It is estimated that 10% to 20% of paragangliomas of the retroperitoneum develop from paraganglioma located along the aortic axis in close association with the sympathetic chain. These tumors often assume a more aggressive clinical course than their adrenal counterparts. Because malignant retroperitoneal paragangliomas can be confused on light microscopy with other tumors of similar histology, such as alveolar soft part sarcoma, rhabdomyosarcoma, and renal cell carcinoma, it is sometimes necessary to use transmission electron microscopy and immunologic stains to make the correct diagnosis.

We describe in this report a case of a retroperitoneal tumor with a variety of histologic features which could be classified as a malignant retroperitoneal paraganglioma only after careful examination by electron microscopy.

Case Report

A 66-year-old black man was admitted to The Mount Sinai Hospital for evaluation of an abdominal mass. The patient was well until one month prior to admission, when he developed abdominal discomfort, weakness, fevers, tremors, loss of appetite, and a fifteen-pound weight loss. A left upper quadrant abdominal mass was found on physical examination. A barium enema and intravenous pyelogram demonstrated that the mass was extrinsic to the gastrointestinal tract with displacement of the descending colon, left kidney, and left ureter. A bone marrow biopsy was negative for tumor.

Following the diagnosis of an adenocarcinoma of the prostate in 1974, the patient had received thirty-two treatments of radiation therapy. There was a long-standing history of hypertension with

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associated cardiac enlargement for which propranolol hydrochloride (Inderal) and hydrochlorothiazide (Esidrix) were administered. There was a strong family history of hypertension. The patient smoked one pack of cigarettes a day for thirty years until 1967, when he was informed that he had obstructive lung disease. He had dyspnea after climbing one flight of stairs, but reported no pedal edema, paroxysmal nocturnal dyspnea, or orthopnea. He was allergic to penicillin.

On admission, the patient was a well-developed, well-nourished man in no apparent distress. Blood pressure was 132/80 mmHg, temperature 99.6°F, pulse 68/min., respirations 24–26/min. Sclerae were muddy. A palpable right anterior cervical lymph node was tender. No other lymphadenopathy was appreciated. The heart and lungs were essentially normal. Bilateral gynecomastia was noted. The contour of the abdomen was asymmetrical and a large firm mass measuring approximately 15 cm in diameter was palpable in the left upper quadrant. This ovoid mass was not tender and remained fixed during deep inspiration. The margins of the liver and spleen were sharp and distinct from the intraabdominal tumor. Although a normal-sized right kidney was felt through the abdominal wall, the left kidney could not be distinguished from the mass. Bowel sounds were normal and a stool guaiac examination was negative. The prostate was enlarged and firm. A large, left-sided inguinal hernia descended to the bottom of the scrotal sac. Dorsal pedal pulses were weak bilaterally.

Laboratory data on admission were within normal limits except for hemoglobin 10.7 g/dL; hematocrit 34%, ESR 82. A chest x-ray demonstrated an enlarged left ventricle and a questionable infiltrate in the lower lobe of the left lung. A gallium scan revealed nonspecific activity in the neck, right upper quadrant of the abdomen, left flank, and left scrotum suggestive of either lymphoma, metastatic carcinoma, or multifocal abscesses. Sonography of the left testicle was normal.

An upper gastrointestinal series showed a large left-sided abdominal mass compressing and displacing the greater curvature of the stomach toward the right hemidiaphragm. Loops of small bowel were shifted toward the right lower quadrant of the abdominal cavity. There was no evidence of intraluminal defects throughout the gastrointestinal tract. The contour of the left kidney was obscured and the corresponding ureter was kinked downward and medially.

Exploratory laporotomy revealed a large retroperitoneal tumor with metastatic involvement of the liver. The tumor was described by the surgeon as being large and bulky, 18 cm in diameter, and in the retroperitoneal space posterior and slightly superior to the left kidney. Although the tumor was encased by fibrous adhesions, it was separable from surrounding organs. Loops of large and small bowel were adherent to the tumor and displaced toward the lower right quadrant of the abdominal cavity.

Since the neoplasm was considered unresectable, a biopsy was taken from the most viable area.

On the eleventh postoperative day, the patient suddenly became dyspneic, with an arterial PO_2 of 43 mm. A lung scan revealed evidence of a massive pulmonary embolus in the right lung with patchy involvement of the left lung. Shortly thereafter the patient died.

Pathological Findings. On light microscopy, the tumor obtained at surgery had malignant features and was composed of three elements: clear cells; pleomorphic, bizarre, large, eosinophilic cells; and many multinucleated giant tumor cells (Figs. 1–4). The metastatic tumor in the liver ex-

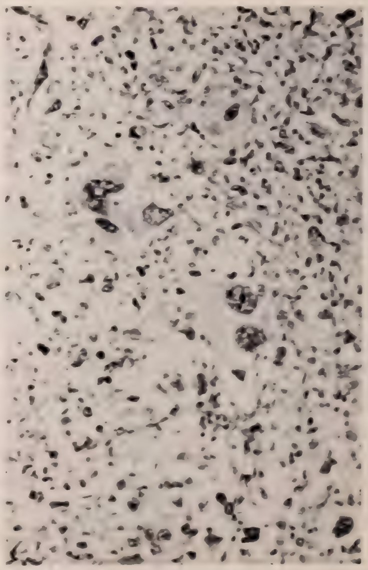

FIG. 1. Anaplastic tumor composed of giant cells with bizarre nuclei; cytoplasm varies from pale granular to clear (hematoxylin and eosin 200×).

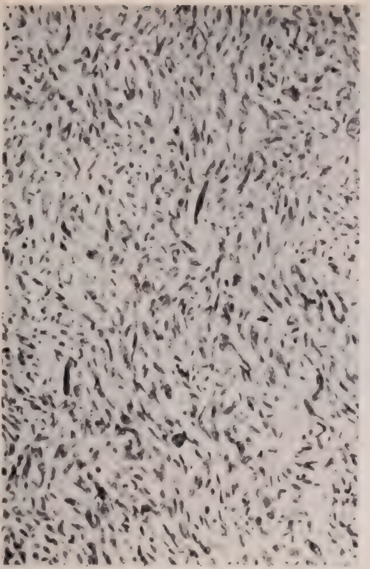

FIG. 2. Portion of tumor exhibiting sarcomatoid variant with spindle-cell pattern (hematoxylin and eosin 300 ×).

hibited a delicate, vascular stroma and zones of hemorrhage. Abundant glycogen was contained in the clear cell elements. Cross-striations or thick 15 nm filaments with or without any organization were not demonstrated; immunohistochemical analysis for myoglobin was negative; therefore the diagnosis of rhabdomyosarcoma was ruled out. The diagnosis was anaplastic malignant tumor with features suggesting rhabdomyosarcoma. However, the possibility of a poorly differentiated renal cell carcinoma could not be excluded.

Electron microscopic study of the biopsy specimen revealed two cell populations. The major population of large cells were electron-lucent and contained a large nucleus with one to two prominent nucleoli. The nucleoli generally had a separation of their components to produce a light-dark appearance, usually in a ring shape (Fig. 5). The remainder of the nucleus had a finely granular appearance. The polygonal and round cells abutted one another with many sites of membrane densities resembling desmosomes and hemidesmosomes where only one membrane contained a density. At the sites where one membrane had a density, there was usually fibrous collagen material resembling basal lamina ma-

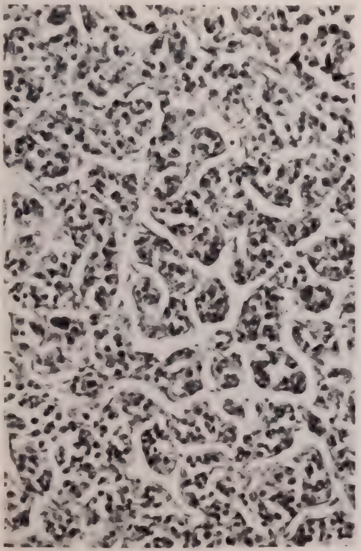

FIG. 3. Organoid variant seen in relatively small portion of neoplasm showing cords of cells with intervening vascular channels (hematoxylin and eosin 300 ×).

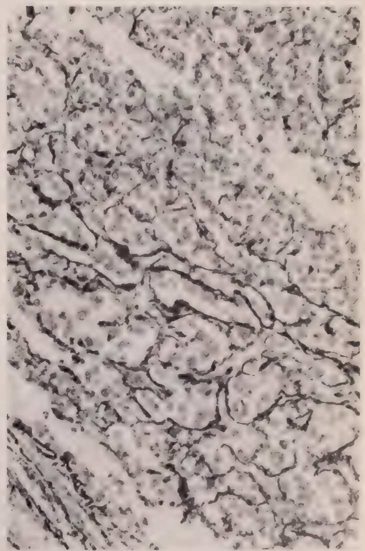

FIG. 4. Reticulin stain in organoid area revealing Zellballen pattern characteristic of paraganglioma (Wilder's reticulin 300 ×).

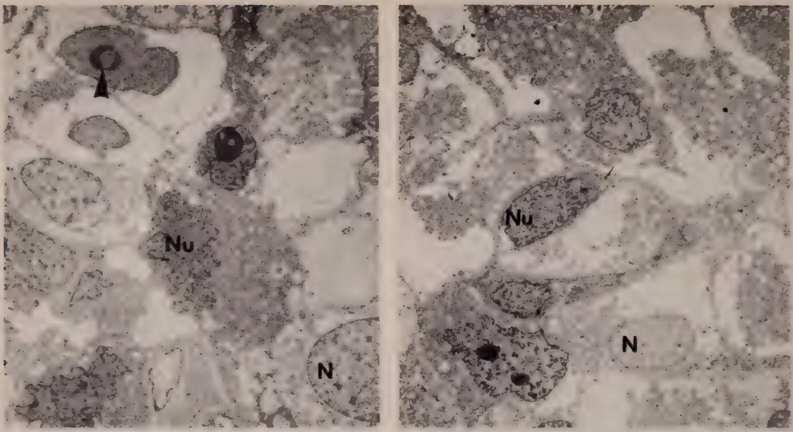

FIG. 5. Low magnification transmission electron micrographs of representative areas of the surgical specimen show two nuclear forms. N is round or oval with a granular appearance and one or two large nucleoli having a ring shape (arrow). **Nu** has an irregular nuclear border with clumped heterochromatin and one or two nucleoli. Cytoplasm of **Nu** cells are filled with mitochondria; cytoplasm of **N** cells have some perinuclear mitochondria, major portion of cytoplasm being electron lucent and apparently empty (uranyl acetate and lead citrate: **left**, 1,430 ×; **right**, 1,430 ×).

terial (Fig. 6). The cytoplasm of most cells contained one area around the nucleus which was filled with mitochondria, most of which were large and swollen; many had a ring or crescent shape (Fig. 7). In the same areas there was granular and smooth endoplasmic reticulum with an absence of Golgi complexes. There were small dense-core granules (110 nm–160 nm) at the cell

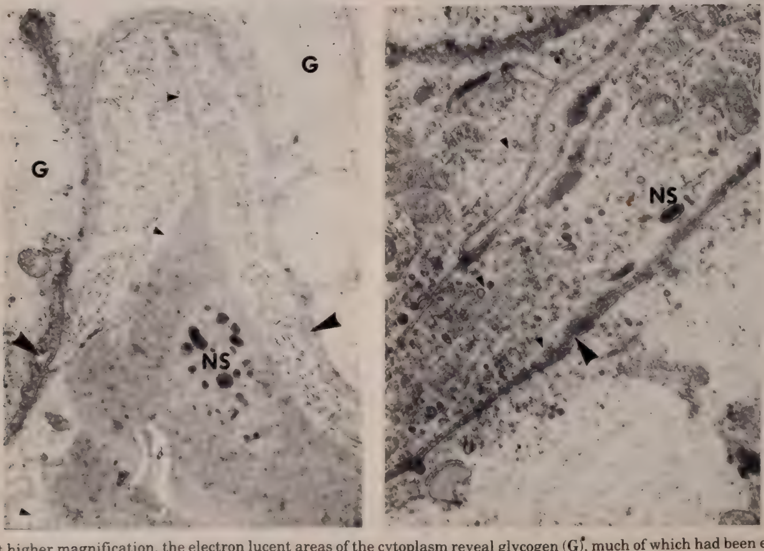

FIG. 6. At higher magnification, the electron lucent areas of the cytoplasm reveal glycogen (G), much of which had been extracted during processing. Many interdigitating processes were apparent and each cell and process was separated from its neighbor by connective tissue matrix (large arrow). Pinocytotic vesicles (small arrow) and dense-core granules (NS) were common (uranyl acetate and lead citrate: **left**, 10,000 ×; **right**, 16,000 ×).

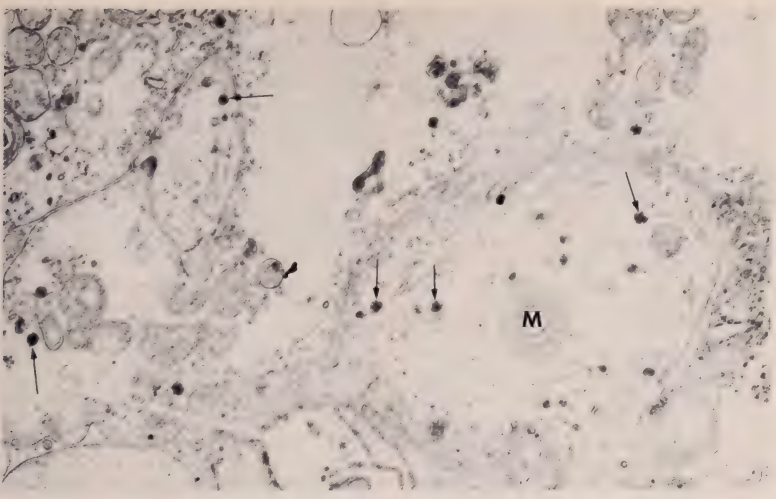

FIG. 7. The cell processes contain signet-ring shaped mitochondria (M), neurosecretory granules (arrows), glycogen, a few microfilaments, microtubules and pinocytotic vesicles (uranyl acetate and lead citrate 12,450 ×).

periphery and in cytoplasmic processes. Some appeared singly, while others were in aggregates. The cell processes contained many 10 nm intermediate filaments, clathrin-coated pinocytotic vesicles, and dense-core granules (Fig. 6). However, the major portion of the cytoplasm contained pooled polymeric glycogen in a rosette arrangement (Fig. 6). A minor population of smaller electron-dense cells was also seen. These cells had large indented and cribriform nuclei with 1 or 2 less prominent nucleoli. The heterochromatin was clumped throughout the nucleoplasm and at the membrane. These cells contained many round and regularly shaped mitochondria in the cytoplasm. Central Golgi complexes were present and dilated granular endoplasmic reticulum traversed the mitochondria. Many capillaries were dispersed among the tumor cells. Study of postmortem specimens contributed little to the ultrastructural interpretation due to the poor preservation of the tissues.

The major findings at autopsy included massive bilateral pulmonary thrombo-emboli and a large retroperitoneal tumor which focally involved the adjacent liver, kidneys, adrenals, and pancreas. The tumor was fluctuant and had a lobulated contour. Extensive cystic degeneration was present, the cut surface exhibiting a red-brown color and several mottled zones of necrosis, hemorrhage, and fibrosis. Generous sampling of the main tumor and foci of metastases displayed histologic findings similar to those found in the surgical specimen. Most sections of the tumor consisted of clear cells, cells with a dense, eosinophilic cytoplasm, and scattered tumor giant cells in a delicate vascular stroma with zones of hemorrhage. After the diagnosis of paraganglioma was made by electron microscopy, a retrospective review of many sections from the biopsy and autopsy specimens revealed a few small foci of tumor with the typical zellballen appearance of paragangliomas only in the autopsy specimen.

Discussion

The most interesting ultrastructural and histologic feature of the case reported here was the abundance of intracellular glycogen. It has been generally accepted that paragangliomas lack cytoplasmic glycogen (4), with the exception of one case (5). However, when the latter tumor was examined ultrastructurally no dense-core granules or microtubules were observed. Other ultrastructural features of neurogenic differentiation, such as the formation of dendritic or axonal processes, were also absent. The diagnosis was based solely on light microscopic features. Ultrastructural analysis of retroperitoneal tumors is most useful, if not an essential diagnostic modality, especially if paraganglioma is a part of the differential diagnosis. Further, it can now be accepted that paragangliomas have the metabolic capacity to produce glycogen and in large amounts.

Ultrastructural analysis of this neoplasm ruled out a variety of tumors which have been described in the retroperitoneum, including liposarcoma, carcinoid, malignant schwannoma, hemangiopericytoma, embryonal rhabdomyosarcoma, angiosarcoma, synovial sarcoma, and fibrous histiocytoma. Most of these neoplasms can be identified in histologic sections. Electron microscopy and immunofluorescent studies may be necessary in difficult cases such as the one described in this report. Rhabdomyosarcoma, fibrosarcoma, and alveolar soft-part sarcoma were eliminated based on nuclear and cytoplasmic features. Since myosin thick filaments (15 nm) and microfilament organization or crystalline inclusions were not present, the diagnosis of rhabdomyosarcoma and alveolar soft-part sarcoma were also eliminated. The absence of true desmosomes might suggest the possibility of malignant lymphoma. However, this diagnosis was excluded by the presence of cells containing abundant glycogen, basement membranes, and dense-core granules. Carcinoid was ruled out by nuclear features, the presence of glycogen and long cytoplasmic processes. A tumor of neuroectodermal origin, possibly a glycogen-rich neuroblastoma, was considered, but the extreme pleomorphism and absence of a rosette pattern precluded this diagnosis. All the ultrastructural features, except for the presence of abundant glycogen, were consistent with a diagnosis of paraganglioma. We were able to find another case of a retroperitoneal nonchromaffin paraganglioma which similarly contained glycogen. However, the diagnosis was based only on light microscopy (5).

Tumors deriving from the neural crest, such as extraadrenal paragangliomas (formerly designated nonchromaffin paraganglioma or chemodectoma), are described in a recently published book devoted to the subject (4). According to the authors, nonfunctioning retroperitoneal paragangliomas are uncommon. In fact, tumors and tumorlike conditions arising in the retroperitoneal space are rare and account for only one in 11,800 general hospital admissions (5). Lymphomas comprise one third of all malignant retroperitoneal tumors and are generally considered manifestations of a systemic disease. Apart from liposarcomas and lymphomas, fibrosarcomas and leiomyosarcomas are the next most common primary malignant retroperitoneal tumors.

The patient reported here falls within the upper limit of age for patients having retroperitoneal paragangliomas. The age of patients with paragangliomas usually ranges from 5 years (6) to 72 years (7), the average age being 37 years (4). However, in a review of 12 patients carefully studied for retroperitoneal paragangliomas, the median age was 43.2 years (8). Incidence by sex is approximately equal (4). In breakdowns by race, whites predominate, but tumors may also occur in blacks (9–13) and orientals (14).

Many patients with retroperitoneal paraganglioma are asymptomatic since the tumors are nonfunctioning (4); other patients have abdominal pain (15, 16), back pain (17), or a palpable mass.

There is a higher incidence (40%) of metastasis from retroperitoneal paragangliomas than from other extraadrenal paragangliomas (4). The tumor is spread via lymphatic and hematogenous routes to abdominal and thoracic sites (4). The histology of these metastatic paragangliomas have a benign appearance similar to those that do not disseminate (6, 12, 15, 17, 18). The number of mitoses has little value in predicting the aggressiveness of the tumor and the outcome of the clinical course.

Acknowledgments

The authors thank Steve Massardo for his technical assistance with the electron microscopy, Norman Katz for the photographic portions, and Maria E. Becerril for typing the manuscript.

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Submitted for publication June 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Gastric Leiomyosarcoma Diagnosed on Chest Roentgenogram: Importance of the Stomach Bubble

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Abstract

The diagnosis of gastric leiomyosarcoma was first suspected on noting a smooth mass in the stomach bubble on the admission posteroanterior chest roentgenogram of a patient with upper gastrointestinal bleeding. Careful examination of the stomach bubble may be helpful in the diagnosis of gastric neoplasm, achalasia of the esophagus, and subpulmonic effusion.

Although the gastric air bubble is almost invariably present in erect chest roentgenograms, it is minimally discussed in most chest radiology textbooks. We report the first case of a gastric leiomyosarcoma initially suspected on posteroanterior chest roentgenogram, and review the importance of careful examination of the stomach bubble in the diagnosis of gastric neoplasm, achalasia of the esophagus, and subpulmonic effusion.

Case Report. A 68-year-old man was admitted to the hospital because of epigastric pain, hematemesis, and melena. Three months prior to admission the patient began taking sulindac (Clinoril) for osteoarthritis of the right hip.

He reported no excessive alcohol abuse, anorexia, weight loss, severe epigastric pain, or previous gastrointestinal hemorrhage.

He was a pale, anicteric man with orthostatic hypotension and resting tachycardia. The abdomen was mildly tender to deep palpation of the periumbilical area without rebound tenderness, organomegaly, or palpable masses; bowel sounds were hyperactive. A rectal examination revealed tarry stools which were strongly guaiac-positive. A nasogastric tube aspirate contained coffee-ground material which was also guaiac positive and which cleared rapidly with iced-saline lavage. Initial laboratory data included hemoglobin 7.5 g/dl, hematocrit 22.7%, white blood cell count 17,000/cu mm (69% segmented neutrophils, 21% lymphocytes, 3% eosinophils, 1% nonsegmented neutrophils, 6% monocytes), platelets 150,000/cu mm. SMA 18 was within normal limits. Prothrombin time was 15.8/13.2 sec. The admission chest roentgenogram (Fig. 1) revealed clear lung fields and borderline cardiomegaly. A 5-cm, smooth, well-circumscribed mass in the lateral portion of the stomach bubble was noted. A tentative diagnosis of gastric leiomyosarcoma was made.

The patient received 5 units of packed red blood cells and the hematocrit stabilized at 35%. Upper gastrointestinal endoscopy confirmed the presence of a large mass in the greater curvature of the fundus of the stomach; the mass was ulcerated, covered by otherwise normal-appearing mucosa, and hard on palpation with the closed biopsy forceps. Wedge resection of the gastric lesion was subsequently performed. Histologic diagnosis was leiomyosarcoma. The postoperative course was uneventful.

Discussion. In this case, the presence on the chest roentgenogram of a large, smooth mass in the fundus of the stomach favored a submucosal lesion. Smooth muscle tumors are the most common nonepithelial gastric neoplasms, and they frequently present with significant upper gastrointestinal hemorrhage (1). Large smooth-

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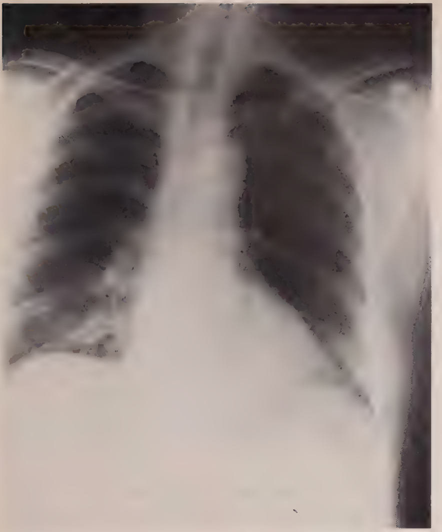

FIG. 1. Admission chest roentgenogram demonstrating large, well-circumscribed mass in stomach bubble.

muscle tumors are more likely to be malignant than smaller lesions (2). In this case, therefore, thorough evaluation of the admission chest roentgenogram, in conjunction with the clinical picture, strongly suggested the correct final diagnosis. This represents, to our knowledge, the first reported example of a gastric leiomyosarcoma originally suspected because of an abnormality of the stomach bubble on a chest roentgenogram. The value and importance of careful examination of the stomach bubble has been previously pointed out (3–6).

Normally the gastric air bubble lies adjacent to the undersurface of the left hemidiaphragm. In 88% of 500 normal chest roentgenograms reviewed by Felson (7), the top of the gas shadow was within 1 cm of the dome of the left hemidiaphragm. The interposition of any structure between the diaphragm and the fundus of the stomach will displace the bubble downward. In addition, when a density obliterates the shadow of the left hemidiaphragm, the stomach bubble may indicate the location of the left hemidiaphragm. In the lateral chest roentgenogram, the presence of the stomach bubble close under one hemidiaphragm indicates that it is the left hemidiaphragm (6).

Abnormalities of the stomach bubble on erect chest roentgenogram may be categorized into three groups: (a) completely absent bubble, (b) abnormal relation to the left hemidiaphragm, and (c) abnormal contour. The three most common abnormalities corresponding to these three groups are achalasia of the esophagus, left subpulmonic effusions, and gastric neoplasms.

In achalasia, absence of the stomach bubble on erect chest roentgenogram (Fig. 2) is a useful diagnostic sign (8–11). In one retrospective study, Orlando et al (12) reviewed 24 cases of documented, untreated achalasia of the esophagus and found that 50% (12/24) of the patients had no gastric air bubble on erect chest roentgenograms compared to 0% (0/25) in asymptomatic control subjects.

The most common cause for an increase in the space between the base of the left lung and stomach bubble is a collection of fluid between the diaphragm and the lung, that is, a subpulmonic effusion (Fig. 3). Common causes of subpulmonic effusions include congestive heart failure, neoplasms, hepatic insufficiency, and infections. More rarely, a similar radiologic appearance can be produced by conditions below the diaphragm which depress the stomach bubble, such as subphrenic abscess, splenomegaly, and large left lobe of the liver (13).

Finally, a change in the normally smooth, sym-

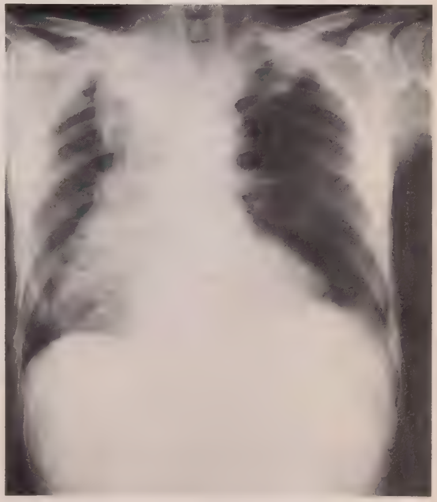

FIG. 2. Chest roentgenogram demonstrating absence of stomach bubble with large right parasternal density. Confirmed achalasia of esophagus.

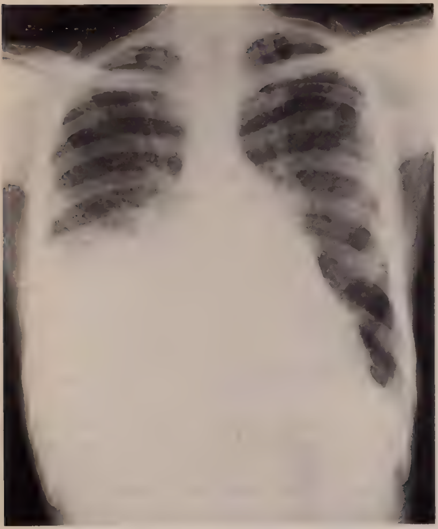

FIG. 3. Chest roentgenogram demonstrating increase in space between base of left lung and stomach bubble. Documented subpulmonic effusion.

metric, downwardly concave shape of the stomach bubble suggests gastric neoplasm, either benign or malignant (4, 5). As originally pointed out by Kirklin and Gilbertson (3), a mass which projects from the medial wall into the gas bubble may be seen as the mass itself or as a change in the contour of the air bubble causing flattened, irregular, even convex changes. In addition, the mass may occasionally cause the disappearance of the bubble or an increase in the distance between the base of the left lung and the bubble.

Fundoplication for hiatal hernia repair may result in a defect closely resembling a smooth, well-circumscribed mass in the stomach bubble and should be included in the differential diagnosis of masslike lesions in this area (14).

Systematic study of a simple chest roentgenogram, including evaluation of the gastric air bubble, can provide useful information and may, on occasion, lead to an earlier diagnosis of asymptomatic and symptomatic lesions such as gastric neoplasms.

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Submitted for publication July 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Folic Acid and Vitamin B_{12} in Long-Term Anticonvulsant Therapy

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Abstract

Serum folate and vitamin B_{12}, determined by protein-binding radioassay, and mean corpuscular volume (MCV) of erythrocytes were measured in a group of 100 nonalcoholic (occasional social drinking only) epileptic outpatients. Correlations were calculated between these parameters and duration of treatment, number of drugs received, and serum level of drugs. The radioassay method for serum folate yielded results comparable to those obtained by microbiological methods. Most of the decrease in serum folate took place during the first five years of treatment. Polypharmacy was the most significant determinant of serum folate depletion. MCV values were significantly correlated with serum folate, and the temporal pattern of increase in MCV mirrored the decreases in folate. Radioassay measurements of serum vitamin B_{12} differed from microbiological measurements.

Chronic toxic effects of drugs tend to be less readily recognized than acute effects, and this has been the case with the anticonvulsants. The importance of the study of these chronic effects derives from the high incidence of epilepsy, estimated to be 6.5–6.9/1000 in the United States and Europe (1), and the fact that most epileptics must continue treatment for years or life. A comprehensive review of the toxicity of long-term treatment with antiepileptic drugs has been presented by Reynolds (2). Side effects include peripheral neuropathy, psychiatric disturbances, encephalopathy, metabolic bone disease, enzyme induction in the liver, alterations in connective tissue, skin, and endocrine system, and immunological disorders. Following the recognition of megaloblastic anemia as a toxic effect of long-term anticonvulsant therapy by Mannheimer et al in 1952 (3), a number of studies in the nineteen sixties and seventies established that subnormal serum folate levels were present in 27% to 91% of epileptics in such long-term treatment, but some authors failed to find a correlation between folate levels and drug dosage or duration of treatment (2, 4). Macrocytosis in peripheral blood occurs in up to 53% and megaloblastic changes in bone marrow occur in up to 38% of such patients. Anticonvulsant-induced folate deficiency is established as the cause of the rare megaloblastic anemia occurring in less than 1% of epileptic patients, but the relationship between folate depletion and macrocytosis or megaloblastic changes in bone marrow has been disputed (2). The most interesting aspect of folate deficiency in epileptic patients is its association with psychiatric disturbances, ranging from irritability to schizophrenialike psychosis and severe depression (5–7).

The purpose of the research reported here was to study the temporal pattern of folate depletion and the relationships of serum folate with anticonvulsant drugs, with mean corpuscular volume (MCV) of erythrocytes, and with serum vitamin B_{12} in a population of well-nourished, nonalcoholic (occasional social drinking only) outpatient epileptics. In contrast to previous studies, radioassay methods were used.

Subjects and Methods

One hundred chronic epileptic outpatients regularly followed in the Epilepsy Clinic of Primero de Octubre Hospital were randomly selected from among patients whose serum folate determinations were available. Ages ranged from 7 to 70

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years (mean, 27.6 years; SD, 14.4 years). All patients were receiving long-term anticonvulsant therapy consisting of phenytoin (82 cases; 24 alone, 58 with other drugs), phenobarbital (57 cases), primidone (25 cases), or other drugs (22 cases), including carbamazepine, sodium valproate, ethosuximide, trimethadione, and clonazepam. Patients taking more than the occasional alcoholic drink were excluded. The average duration of epilepsy was 12.7 years (SD 6.99 years). A group of 100 healthy hospital workers and blood donors, ranging in age from 16 to 65 years (mean, 32.1 years) was used as the control.

Serum folate was measured by competitive protein-binding radioassay, utilizing Dualcounts kits purchased from Diagnostic Products, Los Angeles. The radioassay procedure is based on competition at pH 9.5 of endogenous folates and ^{125}I pteroylglutamic acid for beta lactoglobulin, the specific folic acid binding protein in milk.

In 86 cases, vitamin B_{12} was determined in the same blood sample with the same kit. During the period when this study was carried out the kit used nonpurified intrinsic factor as a binder.

Erythrocyte MCV (determined by Coulter Counter) and serum levels of phenytoin and phenobarbital (measured by gas chromatography) were included in the statistical calculations only when the tests had been carried out within six months of the date of folic acid determination.

Nonparametric methods were used in statistical calculations because of the nonnormal distribution of serum folate and vitamin B_{12} in the population.

Results

The distribution curves of serum folate concentration in the epileptic and control populations are asymmetric (Fig. 1). When compared by the Wilcoxon sum of rank test, the two groups were different ($p < 0.001$). The epileptic group had a much lower mean serum folate concentration (5.16 ng/ml, SD 2.96 ng/ml) than the controls (mean 9.44 ng/ml, SD 4.14 ng/ml). The lowest serum folate in the control group was 3.05 ng/ml; twenty-two epileptic patients had serum concentration below that value. Serum folate concentrations over 3.65 ng/ml were present in 95% of the control group; 42% of the epileptic group measured below that value.

Figure 2 shows that serum folate concentrations decreased in significant inverse correlation with duration of treatment, but scattering was marked and after as many as 20 years of treatment some patients maintained values in the

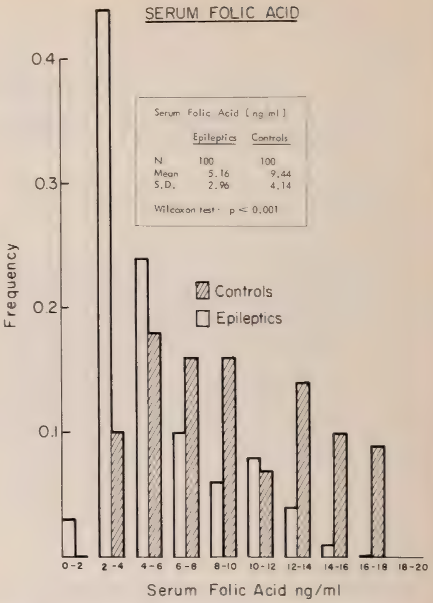

FIG. 1. Distribution (nonnormal) of serum folate concentrations in control and epileptic populations. Comparison by Wilcoxon rank sum test.

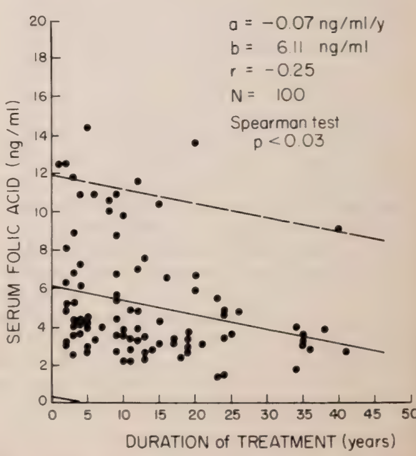

FIG. 2. Serum folate versus duration of anticonvulsant treatment. Figures are for the equation $y = ax + b$. Values fall outside 95% confidence limits (broken lines) because of nonnormal distribution of serum folate. Correlation is significant by Spearman rank test.

normal range. Most of the decrease in serum folate occurred during the first five years; the slope of the folate-versus-time plotting for the 32 patients in treatment for less than five years was −0.57 ng/ml/year, in contrast to −0.02 ng/ml/year for the 48 patients in treatment for more than ten years.

The serum concentrations of folic acid were inversely related to the number of different drugs taken (Table I). Folate levels showed statistically significant correlation ($p < 0.02$) with serum levels of phenytoin (62 cases) as measured by Spearman rank correlation test (rho, −0.315), but no significant correlation with the serum levels of phenobarbital (42 patients) was found (Spearman rho, −0.218). Serum levels of phenytoin ranged from less than 1 mg/ml to 44 mg/ml, with mean 14.4 mg/ml and SD 9.8 mg/ml. Serum levels of phenobarbital, derived from phenobarbital or primidone, ranged from less than 1 mg/ml to 63 mg/ml (mean 25.2 mg/ml, SD 15.8 mg/ml).

TABLE I

Number of Drugs Taken and Serum Folate and Mean Corpuscular Volume of Erythrocytes

No. of drugs	Serum folate (ng/ml)			Mean corpuscular volume (fl)		
	N	Mean	SD	N	Mean	SD
1	33	6.04	3.47	21	87.4	4.6
2	47	4.98	2.61	41	91.3	4.8
3 or more	20	4.11	2.32	18	93.0	5.5
			Wilcoxon rank sum test			
			1 drug versus 3 drugs			
	$p < 0.05$				$p < 0.002$	
			1 drug versus 2 drugs			
	NS				$p < 0.01$	

MCV was normally distributed both in controls (mean 87.5 fl, SD 4.3 fl) and in the 86 epileptic cases tested for it (mean 90.7 fl, SD 5.3 fl), the difference between the two groups being highly significant ($p < 0.001$).

A significant inverse correlation was found between serum folate and MCV in the epileptic group (Fig. 3). A similar inverse correlation, also significant at the 0.05 level, was observed in controls.

MCV increased with increased number of drugs taken (Table I) and correlated with duration of treatment (r, 0.40; $p < 0.05$; slope, 0.22 fl/year). Here again most of the increase occurred during the first five years of treatment; the slope for the 40 patients treated for more than ten years is 0.097 fl/year, but for the 23 patients with less than 5 years it is 1.75 fl/year.

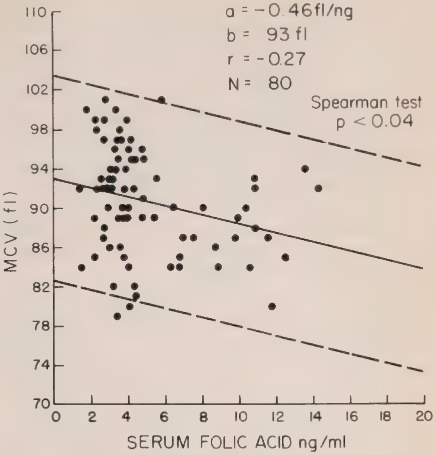

FIG. 3. Serum folate versus mean corpuscular volume of erythrocytes in epileptic group. Figures are for the equation $y = ax + b$. Values fall outside 95% confidence limits (broken lines) because of the nonnormal distribution of serum folate. Correlation is significant by Spearman rank test.

Sex and age were not significant in relation to serum folate levels.

The distribution of serum vitamin B_{12} was not normal in either the control or the epileptic populations. Surprisingly, vitamin B_{12} levels appeared to be significantly higher ($p < 0.001$) in the epileptic group (mean 754 pg/ml, SD 239 pg/ml) than in the controls (mean 590 pg/ml, SD 199 pg/ml). No significant correlations were found between vitamin B_{12} levels and duration of treatment, number of drugs received, or serum folate levels.

Discussion

Radioassay methods for the determination of folate have been criticized because of the widely different results obtained with various folate derivatives and their polyglutamate forms, in contrast with the more uniform results of microbiological assays (8). In serum, however, 5-methyltetrahydrofolate monoglutamate is the only quantitatively significant form (4), and this is equally well measured by either method (8). In this series, 42% of the epileptic group have serum folate concentrations below the 5th percentile when measured by competitive binding radioassay, a result comparable to those obtained with the classic microbiological methods when applied to an epileptic population receiving anticonvulsant drugs (5–7, 10–14). Furthermore, the values obtained are biologically significant; the statistical association of low serum folate values with psychiatric disturbances (15) and cerebellar ataxia (16) has been shown for this same series. Klipstein (10) described a higher incidence of subnormal serum folate in patients in anticonvulsant drug therapy for more than five years. No temporal relation was found by Malpas, Spray, and Witts (9). Our results show that the anticonvulsant-induced decrease in serum folate is a slow process taking place mostly during the first five years of treatment.

The lack of significant association between serum folate and phenobarbital levels, in contrast to phenytoin levels, is not surprising, taking into account the multiplicity of drugs received by the epileptic group. The significant correlation between serum folate and phenytoin, which has also been found by others (17), has sometimes been construed as indicating that phenytoin is the only, or virtually the only, drug responsible for the subnormal folic acid values in epileptic patients. In the group reported on here, however, it appears that polypharmacy is a more significant factor in the production of low serum folate than individual drug levels. In 1958 Hawkins and Meynell found a higher incidence of macrocytosis in patients receiving two drugs (18).

Child et al (19) did not find a correlation between low serum folate and MCV in treated epileptics, but they apparently did not use actual serum folate concentration in their calculations. Our results indicate that such a correlation does exist, but the dispersion of the data does not allow one to substitute the measurement of MCV for the measurement of folate in routine clinical evaluation of epileptic patients in long-term therapy. The temporal pattern of increase in MCV values mirrors the pattern of folic acid decreases.

The mechanisms by which anticonvulsants induce folate depletion in serum, cerebral spinal fluid, and red blood cells are unclear. Proposed mechanisms can be summarized as (a) interference with the intestinal absorption of folates; (b) induction of enzymes in the liver that require and finally deplete folates; (c) interference with the metabolisms of folate coenzymes (2, 4).

The surprising finding of increased vitamin B_{12} in the epileptic group differs from findings in previously published series (9, 12, 14, 20, 21). Kolhause et al (22) have shown that commercial kits for the determination of vitamin B_{12} measured cobolamine and a number of cobolamine analogues of unknown function present in serum, owing to the lack of purity of the intrinsic factor used as binder. Later, Sheppard and Ryrie (23) showed that as serum folates decrease, serum cobolamine decreases but cobolamine analogues in serum increase. These results were obtained in the general population, and it is not known how they apply to anticonvulsant-treated patients. The method used does not permit evaluation of the relative contributions of cobolamine and cobolamine analogues to the elevated values obtained. The occasional epileptic patient shows high vitamin B_{12} in serum when microbiological methods are used (14), in spite of the fact that the cobolamine analogues do not support the growth of microorganisms. The subject deserves further study.

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Submitted for publication April 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

One-Stage Surgery for Bilateral Bullous Emphysema via Median Sternotomy: Report of Three Cases

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Abstract

We report successful bilateral bullectomies through a median sternotomy incision in three patients with giant bullae and severe chronic obstructive lung disease. The demonstration of good perfusion on perfusion lung scanning and relatively well preserved circulation of the compressed lung on pulmonary angiography supported the decision to perform surgery. Median sternotomy is the preferred surgical approach for bilateral bullous disease because of the feasibility of one-stage resection and low complication rate. Our short-term results were good, but long-term results may depend on the severity of underlying lung disease.

In patients with bilateral bullae and severe chronic obstructive lung disease poorly responsive to medical treatment, a major decision is whether surgery should be performed, in view of its high risk and unpredictable results. If surgery is undertaken, what is the preferred surgical approach? We report three patients with bilateral bullae occupying more than 30% of each hemithorax and severe chronic obstructive lung disease who had subjective and objective improvement following one-stage bilateral bullectomies through median sternotomy incisions.

Case Reports

Patient 1. A 23-year-old white woman had a long history of chronic cough and progressively severe dyspnea since childhood. She was regularly treated with bronchodilators, and with steroids and antibiotics during acute exacerbations. She had smoked one pack of cigarettes a day for three years.

The patient was thin and tachypneic at rest. Breath sounds were decreased and occasional wheezes were heard. A chest roentgenogram showed large hyperlucent areas in both lower lung fields and depressed diaphragms. Her Alpha 1 antitrypsin level was normal. The sweat test was negative. Pulmonary function tests showed severe airways obstruction, a large difference between functional residual capacity determined by helium and body box methods, abnormal diffusion capacity, large increase in total lung capacity, hypoxemia, and hypercarbia (Table I). Serial studies documented worsening over a two-year period. Perfusion lung scans showed multiple defects in both lower and right mid upper lung fields, but good perfusion to the remainder of the lungs. A ventilation scan showed defects of both lower lung fields and delay in ventilation of the right upper lung field. A pulmonary angiogram showed large avascular areas in the anterior segment of the right upper lobe as well as in both lower lobes. The lower lobe bullae each occupied more than one third of the hemithorax. The pulmonary vasculature of the right upper lobe was decreased in number and caliber. The vessels appeared well preserved and crowded together in the left upper and mid lung fields (Fig. 1). Data from catheterization showed moderate pulmonary hypertension (Table I).

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Through a midsternal splitting incision the mediastinal pleura was opened and large bullae from both lower lobes and the right upper lobe were removed after placing a GIA stapler at the base of the bullae; a few small blebs were plicated using a 3/0 silk suture ligature. The patient tolerated the procedure well. The pathologic findings were panlobular and bullous emphysema, chronic bronchitis, bronchiolitis obliterans, and moderate pulmonary vascular sclerosis. The postoperative course was complicated by an air leak for two weeks. She was discharged on the 25th day after surgery. Six months after the operation she was able to walk four or five blocks and return to work part time. Pulmonary function tests showed significant improvement (Table I). After that she deteriorated slowly. Three years following bilateral bullectomy she was on a ventilator at home.

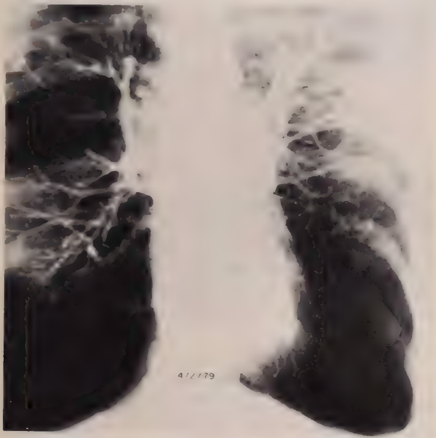

FIG. 1. Preoperative pulmonary angiogram, Patient 1.

TABLE I

Preoperative and postoperative cardiopulmonary data, Patient 1

Study	Pre-operative	6 Months post-operative	Predicted
TLC, L	7.31	6.35	5.09
VC, L	1.40	2.34	3.90
FRC (body box), L	5.95	5.21	3.03
FRC (helium), L	2.24	—	3.03
RV, L	5.75	4.01	1.45
FEV_1, L	0.50	0.59	3.14
FEV_1/FVC, %	36	27	80
Dsb ml/mm Hg/min	13.6	—	23.6
Raw cm H_2O/L/sec	7.17	3.86	2.50
PaO_2 mm Hg	60	76	—
$PaCO_2$ mm Hg	53	43	—
pH	7.32	7.36	—
PA press. mm Hg (mean)	50/15 (35)	—	—
RV press. mm Hg	50/5	—	—

Patient 2. A 65-year-old white woman was well until ten years prior to hospital admission, when she began experiencing increasing shortness of breath on exertion, and productive cough. She had been treated with bronchodilators, and steroids and antibiotics during exacerbations. She also had a history of chest pain on exertion, relieved by nitroglycerin. She smoked two packs of cigarettes per day for 35 years.

On physical examination the patient was in no respiratory distress. Breath sounds were decreased, right more than left. Expiratory wheezes were heard bilaterally. A chest roentgenogram showed bullae occupying more than one third of each hemithorax in both upper lobes and depressed diaphragms. Pulmonary function tests showed severe obstruction of air flow, a large difference between functional residual capacity determined by helium and body box methods, abnormal diffusion capacity, large increase in total lung capacity, hypoxemia, and hypercarbia (Table II). Serial pulmonary function studies showed no improvement. Perfusion lung scan revealed decreased perfusion to both upper lobes and good perfusion of both lower lung fields. Pul-

TABLE II

Preoperative and postoperative cardiopulmonary data, Patient 2

Study	Pre-operative	7 Months post-operative	Predicted
TLC, L	7.24	5.10	4.25
VC, L	1.30	1.98	2.60
FRC (body box), L	6.40	3.71	2.61
FRC (helium), L	3.72	3.63	2.61
RV, L	5.94	3.12	1.63
FEV_1, L	0.47	0.69	1.87
FEV_1/FVC, %	36	37	73
Dsb ml/mm Hg/min	6.05	—	20.2
Raw cm H_2O/L/sec	4.47	4.30	2.5
PaO_2 mm Hg	65	69	—
$PaCO_2$ mm Hg	45	41	—
pH	7.39	7.36	—
PA press. mm Hg (mean)	32/10 (19)	—	—
RV press. mm Hg	32/3	—	—

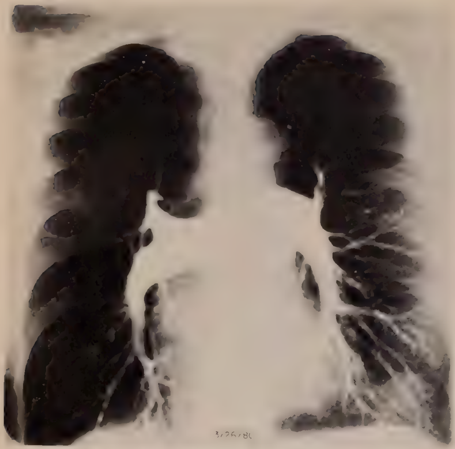

FIG. 2. Preoperative pulmonary angiogram, Patient 2.

monary angiogram showed large avascular areas in both upper lobes. The pulmonary vasculature of the right mid and lower lungs appeared decreased in caliber and number. The vessels were well preserved and crowded in the left mid and lower lung fields (Fig. 2). A coronary angiogram was normal.

Surgical excision of large bullae from both upper lobes was performed through a median sternotomy approach. The patient tolerated the procedure well. The pathologic report was emphysematous bullae. She was discharged on the 17th postoperative day. On followup seven months after surgery she was able to walk five blocks. She developed an incisional hernia which was corrected surgically. Pulmonary function tests showed significant improvement (Table II). She continued to smoke and showed mild clinical deterioration two years after the operation. She was able to walk two blocks.

Patient 3. A 52-year-old white woman was admitted with a five-year history of shortness of breath on exertion without cough. She smoked one pack of cigarettes a day for 35 years. She had been treated with bronchodilators without improvement.

The patient was thin, but in no respiratory distress. Breath sounds were decreased and a few wheezes were heard. Chest ròentgenogram showed hyperlucency of both upper lobes and depressed diaphragms. Pulmonary function studies showed severe airways obstruction, a large difference between functional residual capacity determined by helium and body box methods, large increase in total lung capacity, resting hypoxemia, and hypercarbia (Table III). Serial tests showed no improvement. A perfusion lung scan revealed decreased perfusion to both upper lobes and good perfusion to both lower lung fields. A pulmonary angiogram showed large avascular bullae one half of each hemithorax in both upper lung fields. The vessels appeared well preserved and crowded together in both mid and lower lung fields (Fig. 3).

Surgical excision of the bullae from both upper lobes was performed via median sternotomy. The patient tolerated the procedure well. The pathologic findings were multiple bullae, fibrosis, and chronic inflammation. She was discharged on the twelfth day. Three months after the operation she had increased exercise tolerance and could climb three flights of stairs and walk four blocks. Pulmonary function tests showed significant improvement (Table III). She continued to smoke and showed mild clinical deterioration two years after the operation. She was able to walk two blocks.

Discussion

A bulla is defined as an emphysematous space exceeding one centimeter in diameter (1). Progressive increase in the size contributes to functional impairment by compressing adjacent lung.

TABLE III

Preoperative and postoperative cardiopulmonary data, Patient 3

Study	Pre-operative	3 Months post-operative	Predicted
TLC, L	6.41	5.30	4.87
VC, L	1.05	2.32	3.23
FRC (body box), L	5.73	3.68	2.97
FRC (helium), L	3.31	3.26	2.97
RV, L	5.36	2.98	1.70
FEV_1, L	0.47	0.89	2.44
FEV_1/FVC, %	59	38	75
Dsb ml/mm Hg/min	—	—	—
Raw cm H_2O/L/sec	4.11	2.92	2.5
PaO_2 mm Hg	64	80	—
$PaCO_2$ mm Hg	50	41	—
pH	7.36	7.39	—
PA press. mm Hg (mean)	28/10 (17)	—	—
RV press. mm Hg	28/0	—	—

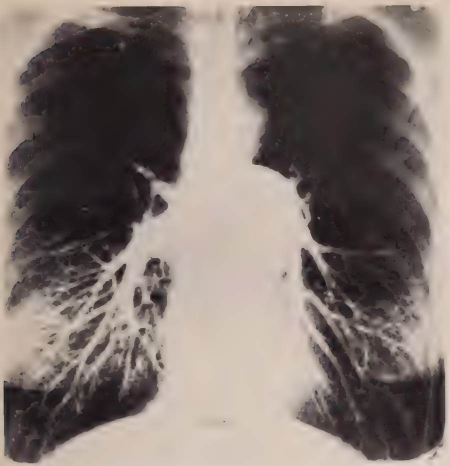

FIG. 3. Preoperative pulmonary angiogram, Patient 3.

Removal of giant bullae (nonfunctioning lung parenchyma) allows the compressed lung to expand and may lead to improved lung function. Perfusion lung scanning and pulmonary angiography have been used to assess the bullae and compressed lung when surgical intervention is considered. Combined generalized and bullous emphysema may be difficult to evaluate even with those procedures.

Previously, surgery was not recommended in patients with bullous disease and advanced diffuse emphysema (FEV_1 less than 30% of predicted), hypercapnia, pulmonary hypertension, and cor pulmonale because of unpredictable results (2). The presence of a large difference in functional residual capacity determined by helium and body box methods suggests that surgery may be helpful (2). Small bullae and advanced generalized emphysema with a characteristic "winter tree" pattern on pulmonary angiography are contraindications for surgery (3). With good operative and postoperative respiratory care, indications for surgery have now been expanded to include patients with severe ventilatory abnormalities and bullae occupying more than 30% of a hemithorax (4, 5).

We initially managed our patients medically but saw no improvement in symptoms and serial pulmonary function tests. Surgery was considered despite severe degrees of obstructive lung disease after documentation of bilateral giant bullae on chest x-ray and a large difference in functional residual capacity determined by helium and body box methods. The demonstration of good perfusion and relatively well preserved circulation of the compressed lung on perfusion lung scanning and pulmonary angiography, respectively, implied preservation of the gas exchange unit of the compressed lung and therefore supported the decision to perform surgery.

The traditional surgical approach to patients with bilateral bullous emphysema has been staged bilateral thoracotomies (2, 6). Disadvantages of this method include two operations and increased pulmonary complications.

We prefer median sternotomy because bilateral bullectomy can be completed in one operation. Midsternotomy has been the standard approach for cardiac surgery over the past 25 years. A number of authors have reported utilization of a median sternotomy incision for simultaneous bilateral pulmonary operations (7). This procedure causes less pain and postoperative ventilatory impairment than lateral thoracotomy (8).

Our short-term results were good, producing subjective improvement in all three patients. Pulmonary function tests showed an increase in the forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), decrease in the large difference in functional residual capacity (FRC) determined by helium and body box methods, decrease in residual volume (RV), total lung capacity (TLC), and airway resistance. Although the FEV_1 improved only minimally, arterial oxygen tension increased and arterial PCO_2 decreased toward normal.

The aim of bullectomy in these patients is rehabilitation rather than cure, and the long-term results will be related to underlying lung tissue. Good long-term results can be obtained in some patients for a number of years (2). Two and a half years following bilateral bullectomy, our first patient deteriorated rapidly after short-term improvement. She is now on a ventilator at home. Our second and third patients continued to smoke and showed mild clinical deterioration two years postoperation. There was no recurrence of bullae on follow-up chest x-ray examinations in any of the patients.

Worthwhile short-term improvement occurs in patients with severe ventilatory impairment after bilateral resection of large bullae. We believe that median sternotomy is the preferred method of surgical approach.

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Submitted for publication January 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Mesenteric Fibromatosis

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Abstract

Two cases of mesenteric fibromatosis are presented. Histologically, the tumors consisted of interlacing bundles of spindle-shaped cells with intervening collagenous fibers, and areas of hemorrhage, necrosis, and moderate inflammatory infiltrate. Ultrastructurally, they were composed of dense fibrous tissue and scattered spindle cells, mostly fibrocytes with a few fibroblasts interspersed. The etiology of these tumors is unknown, but certain associations are discussed.

Mesenteric fibromatosis is a rare, benign condition which may produce intestinal obstruction, bowel perforation (1), or abdominal pain due to infarction of the mass after torsion (2). However, many patients with this neoplasm are asymptomatic. Mesenteric fibromatosis has been associated with Gardner's syndrome and familial polyposis, and may be accompanied by fibrosis, epidermoid cysts, or osteomas (3, 4).

We recently had the opportunity to study two patients with mesenteric fibromatosis who had asymptomatic masses, and document the clinical and pathologic features.

Case 1

A 66-year-old asymptomatic man was admitted to the Veterans Administration Medical Center, Bronx, New York with a large, firm, mobile, nonpulsatile, midabdominal mass. Rectal examination was unremarkable, and blood was not demonstrated in the stool. Barium contrast studies of the entire gastrointestinal tract and intravenous pyelogram were unremarkable. An abdominal sonogram demonstrated a large, mostly solid mass with small cystic areas. Selective celiac artery angiography demonstrated displacement of the vasculature by an avascular mass. An exploratory laparotomy was performed. Two distinct masses within the leaves of the small bowel mesentery were resected with a portion of small bowel. The postoperative course was uneventful.

Pathology. The specimen included a 34-cm segment of small bowel with a large, well-encapsulated 24 × 16 × 8 cm mass within the mesentery. The cut surface was smooth, homogenous, firm, tan-white and glistening, and "criss-cross" trabeculations were seen throughout. A soft, cystic, necrotic 8 × 3.5 × 1 cm area was at one end of the mass (Figure 1). Histologically, the tumor consisted of interlacing bundles of spindle-shaped cells with intervening collagenous fibers (Figure 2). The nuclei were plump with scanty cytoplasm. Mitoses were not seen. The cystic area was necrotic and hemorrhagic, with a moderate amount of inflammatory cell infiltrate.

Case 2

A 30-year-old woman was admitted to The Mount Sinai Hospital for the second time. She had been in good health until two years before, when she developed metrorrhagia, ascites, and pleural effusion. An exploratory laporatomy demonstrated multiple adhesions. Biopsy of the peritoneal adhesions showed fibrous tissue, inflammatory infiltrate, granulation tissue, and starch crystals. Although she had not had prior abdominal surgery, it was subsequently ascertained that she used a starch product as a drying agent for a vaginal contraceptive diaphragm. She was discharged from the hospital and did well until one month prior to this admission for an abdominal mass. A large, midabdominal mass ex-

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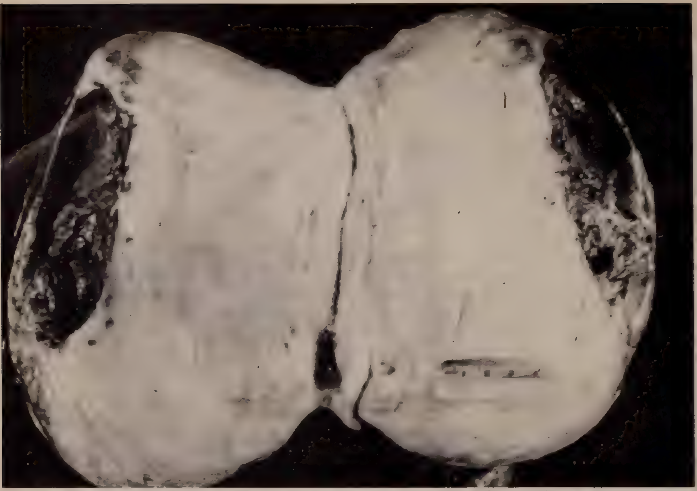

FIG. 1. Large, well-encapsulated mass with smooth, homogenous, tan-white, firm surface and areas of cystic necrosis.

tending from the pelvis to the umbilicus was palpable. The uterus and adnexae were unremarkable. There was no blood in the stool (guaiac test). Barium contrast study of the gastrointestinal tract, intravenous pyelogram, and abdominal sonogram all demonstrated an 11-cm solid mass arising from the pelvis with external compression of small bowel and posterior displacement of the sigmoid. Two masses within the leaves of the small bowel mesentery were resected with a portion of small bowel. The postoperative course was uneventful.

Pathology. The resected specimen consisted of a 160-cm segment of small bowel with attached mesentery. Within the leaves of the small bowel mesentery was a large, well-encapsulated, solid 13-cm mass which infiltrated the bowel wall. On cross section, the tumor was homogenous, firm,

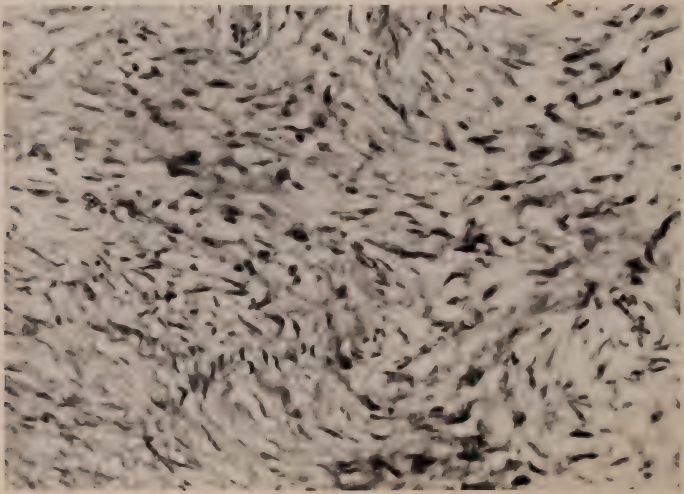

FIG. 2. Photomicrograph of interlacing bundles of spindle-shaped cells (plump nuclei with scanty cytoplasm) with intervening collagenous fibers.

whitish-yellow, with a glistening surface and multiple fibrillar striations. No hemorrhage or necrosis was present. A similar, separate 2-cm nodule was also found within the leaves of the mesentery.

Histologically, the major portion of the tumor consisted of interlacing, wavy trabeculations of fibrocytes. No mitoses were seen. Other areas were mostly composed of collagen. In contrast, variable amounts of inflammatory infiltrate and granulomatous response were present within small nodules surrounding talc granules.

Ultrastructural Studies

Ultrastructurally, the tumors of the two patients were indistinguishable and were composed of dense fibrous tissue characterized by abundant collagen and sparsely scattered spindle cells. The majority of the cell population consisted of fibrocytes (Figure 3): these had large oval indented nuclei, little heterochromatin, and a single prominent nucleolus. The cytoplasm contained rough endoplasmic reticulum, a few oval or round mitochondria, and a few Golgi complexes. Fibroblastic cells were present (Figure 4) but were only a minor population. The fibroblastic cells had a greater cytoplasmic volume, and nuclei with considerable heterochromatin; nucleoli were scarce. The cytoplasm contained abundant rough endoplasmic reticulum, frequently dilated, and many Golgi complexes, as well as free ribosomes and several mitochondria.

Discussion

In their review of primary mesenteric tumors, Yannopoulos and Stout (5) found mesenteric fibromas to be the most common of the solid tumors. In their series, patients were aged six days to 73 years; there was no sex predominance. Typically, small mesenteric fibromas tend to be asymptomatic, whereas larger ones produce a wide range of complaints, including a sensation of abdominal pressure and fullness. Symptoms may also be due to tumor compression of adjacent organs, and patients may have crampy abdominal pain with nausea and vomiting, change in bowel habits, weight loss, and dysuria (2).

Mesenteric fibromatosis most often arises within the small intestinal mesentery (5), the highest frequency of lesions being in the ileal mesentery (3). Less commonly, these tumors are found in the gastrohepatic mesentery, the mesocolon (3), and the gastrosplenic ligament (5).

The histologic diagnosis of mesenteric fibromatosis is based on the presence of interlacing bundles of parallel fibroblasts and typical spindle cell fibrocytes which assume a trabecular pattern. Variable amounts of collagen and inflammatory cells are present. Mitoses are not found. Ultrastructurally, the spindle-shaped fibrocytes con-

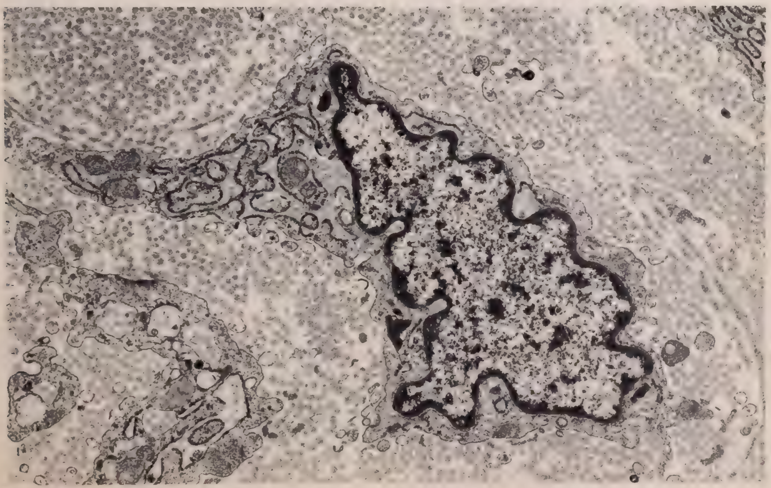

FIG. 3. Transmission electron micrograph of fibrocyte surrounded by collagen bundles. Attenuated cytoplasm contains mainly dilated granular endoplasmic reticulum, with a few mitochondria and some 10 nm intermediate filaments. Nucleus is indented and has substantial rim of heterochromatin. (Uranyl acetate and lead citrate ×13,500.)

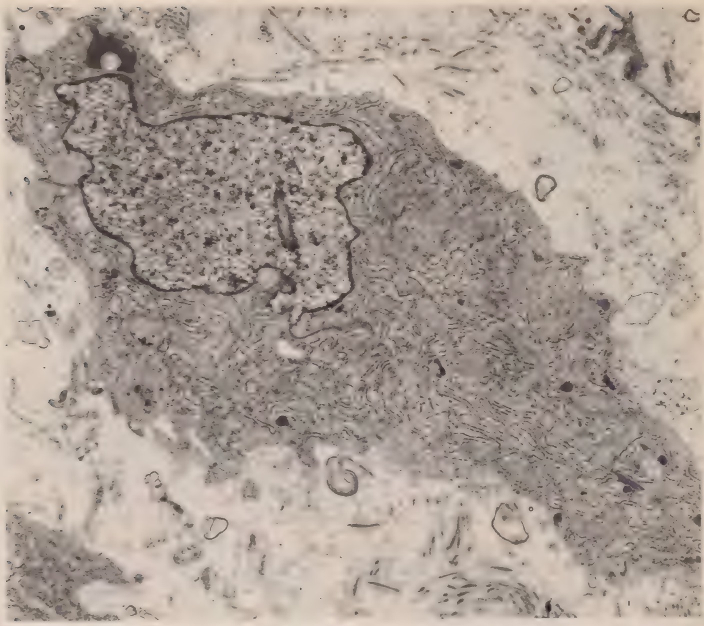

FIG. 4. A few fibroblasts in areas of tumor mass are distinguished from fibrocytes by increased cytoplasmic volume, narrow rim of peripheral heterochromatin, and large numbers of Golgi complexes. Fibroblasts contain substantial amount of undilated, granular endoplasmic reticulum but not as much as the well-differentiated fibrocyte. (Uranyl acetate and lead citrate × 7000.)

tain large nuclei, often indented, with a medium-sized nucleoli. The cytoplasm is filled with dilated endoplasmic reticulum with occasional Golgi complexes, mitochondria, and occasional lipid vacuoles.

The pathogenesis of mesenteric fibromatosis is unknown. It may occur as part of a constellation of physical findings, as described above. In Case 2, talc particles were associated with the fibroma. The tissue response to talc is known and the talc from surgical gloves is well-recognized as a cause for the postoperative development of peritoneal adhesions and tissue granulomas at the site of operation (6). Experimental studies in animals have added significantly to our understanding of the biological effects of talc. The fibrotic response of tissue to talc is a function of particle size, administered dose, and time (7, 8).

Talc particles were not detectable histologically or ultrastructurally in either the large tumor of Patient 2 or the tumor of Patient 1. Although the finding of talc particles in the small nodules in Patient 2 suggest a causal relationship between talc and fibromatosis, there is no other evidence to support this speculation and we must regard these lesions as de novo proliferations of fibroblasts and fibrocytes.

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Submitted for publication March 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Ophthalmologic Notes

Keith M. Zinn, M.D., Editor

Recurrent Massive Periretinal Proliferation in a Double Perforating Injury with a Metallic Intraocular Foreign Body: Case Report

KEITH M. ZINN, M.D.

Massive periretinal proliferation is probably the most common cause of failure in retinal detachment surgery today. Proliferative vitreoretinopathy (PVR) or massive periretinal proliferation (MPP) is caused by the proliferation of cellular membranes within the vitreous gel and usually on the inner surface of the retina. MPP membranes can also grow along the outer surface of the retina (subretinal space) as well as within the neurosensory retina, creating tractional as well as rhegmatogenous retinal detachments. These retinal detachments are not always readily repaired using scleral buckling surgical techniques exclusively, but usually require vitrectomy surgery as well.

The origin of the cells responsible for MPP membranes has been described in the literature and includes ciliary epithelium (1, 2), endothelial cells (3), fibrocytes (4, 5), retinal pigment epithelium (6, 7), and retinal glial cells (8–10). Other studies have incriminated whole blood (11–14), platelets (14, 15), leukocytes (16), and lymphocytes (17, 18) in vitreous membrane formation.

The case of recurrent MPP in a double perforating injury to the globe with a magnetic intraocular foreign body is presented to depict the surgical problems in managing this type of ocular injury and the persistence necessary in some cases to achieve a successful result.

Case Report

A 32-year-old Hispanic man was struck in the left eye with several metallic fragments (Fig. 1) while using a metal hammer on September 21, 1979.

Ocular Findings. Ocular findings several hours after the injury were as follows:

Visual acuity was 20/30 +3 in the right eye and barely 20/400 in the left eye. Manifest refraction could not improve the visual acuity in either eye.

Extraocular motility studies revealed a full rotation of either globe in all standard fields of gaze and the eyes appeared to be grossly straight in the primary position of gaze.

Cranial nerve function II, III, IV, ophthalmic branch division of V, VI and VII were grossly intact bilaterally, but there appeared to be some reduction in the visual field in the left eye. Formal visual field testing could not be performed in the left eye due to the poor vision in that eye at that time.

The lids, lacrimal gland apparatus, and ocular adnexae were entirely within normal limits on the right, and the patient had a 2-mm laceration in the nasal portion of the left upper lid. In addition, 3+ periorbital edema was present in the left upper and to a lesser extent in the left lower lid region. There was 3 mm of ptosis of the left upper lid. The palpebral and bulbar conjunctiva, cornea, and sclera were within normal limits in the right eye, but in the left eye a bulbar conjunctival hemorrhage extended from the limbus, posteriorly, for at least six or eight millimeters in the superonasal quadrant. The corneae appeared to be grossly clear bilaterally.

The intraocular pressures were 20 mm Hg in the right eye and 19 mm Hg in the left eye by applanation tonometry.

Slit lamp examination of the anterior chambers revealed them to be clear, of moderate depth with

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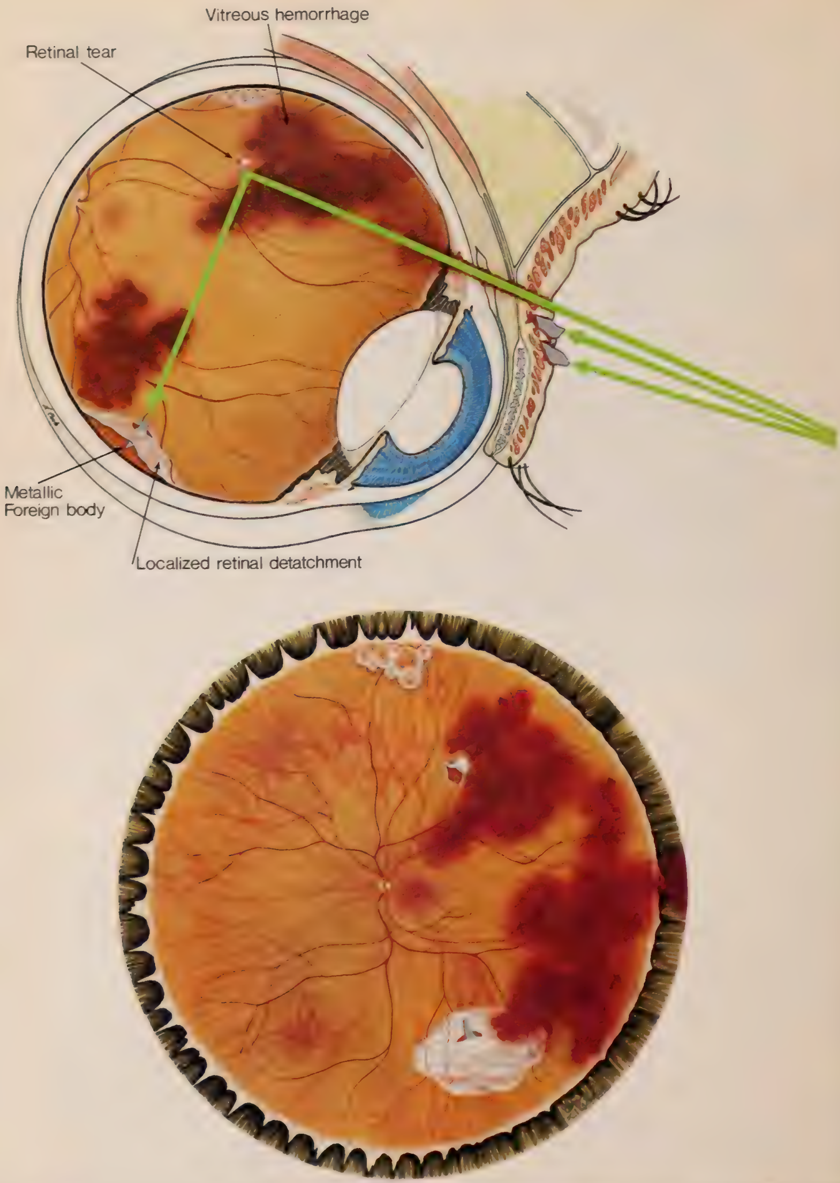
Vitreous hemorrhage
Retinal tear
Metallic
Foreign body
Localized retinal detatchment

FIG. 1. **Top:** Three-dimensional cutaway view of left globe and upper lid. Green arrows show probable path of metallic fragments into the lid and the eyeball resulting in hemorrhage, retinal tears, and localized retinal detachment. **Bottom:** Two-dimensional fundus painting of vitreous hemorrhage retinal tears and localized retinal detachment with metallic foreign body embedded in retina and choroid; several small intravitreal air bubbles are also present superiorly. *Artist: Laurel Cooke.*

Grade III open anterior chamber angles and 1+ pigmentation of the trabecular meshwork bilaterally. There was trace to 1+ cells and flare in the left anterior chamber. The irides were brown bilaterally and the pupils were approximately 6 to 7 mm in diameter, fixed and nonreactive to light or accommodative targets due to previously instilled mydriatic medications earlier in the day.

The right lens was clear and unremarkable but did have a Mittendorf dot (embryologic remnant of the hyaloid vascular system) just superotemporal to the visual axis. The left lens was grossly clear centrally; some minute cataract opacities (minimal) were present in the superonasal quadrant of the lens. The right vitreous cavity was clear and unremarkable, with an incomplete posterior cortical vitreous detachment. The left vitreous body had a hemorrhage; 2 to 3+ RBCs were present in the vitreous gel. There was a substantial amount of vitreous hemorrhage in the superotemporal as well as in the inferotemporal quadrant (Fig. 1) of the left eye.

Funduscopic examination revealed well-demarcated optic nerve head margins with good central physiologic cups oculus uterque (OU). The cup: disc ratio, in the horizontal meridian, was approximately 3:2 OU. The foveal reflex was crisp with normal macular pigmentation in the right eye. The macular region in the left eye could not be seen clearly because of some overlying vitreous hemorrhage but appeared to be intact.

Peripheral indirect ophthalmoscopy in the right eye did not reveal any retinal breaks or tears and a zone of 1+ white with pressure extended from the equator anteriorly to the ora serrata and ran for 360 degrees in the right eye. Peripheral indirect ophthalmoscopy of the left eye revealed a retinal tear near the equator at the 12 o'clock meridian with some overlying vitreous hemorrhage, but the retina appeared to be attached in the region of this tear (Fig. 1). In the inferotemporal quadrant there was a piece of steel that appeared to be approximately 4 to 5 mm in length and 2 to 3 mm in width embedded in the retina and choroid with a surrounding localized retinal detachment and some overlying vitreous hemorrhage (Fig. 1). The temporal macular area was also partially obscured by vitreous hemorrhage.

A and B scan ultrasonography revealed diffuse vitreous hemorrhage as well as a localized retinal detachment and an intraocular metallic foreign body embedded in the inner wall (retina and choroid) in the inferotemporal quadrant of the left eye.

Surgical Procedures. The patient was admitted to the hospital and underwent retinal detachment surgery (trapdoor scleral buckle) with removal of the intraocular metallic (steel) foreign body from the retina and choroid of the left eye. An additional retinal break was treated with cryopexy, several steel fragments were removed from the left upper lid, and the lid laceration was repaired. At the end of the operation x-rays taken in the operating room showed complete removal of all intraocular as well as lid metallic foreign bodies from the left eye.

Postoperatively the patient did well until three days after the operation, when the left eye began to develop intraocular membranes that led to a redetachment of the retina. This necessitated a second operative procedure on September 25, 1979; pars plana vitrectomy was performed to remove hemorrhagic material and new membranes that were forming in the vitreous cavity and on the surface of the retina within the eye. These membranes were pulling on the retina and causing the new retinal detachment. The retinal tear site at the 12 o'clock meridian was buckled closing the retinal tear and the retina was reattached in the left eye. The patient was discharged from the hospital on October 1, 1979.

The patient was next seen in our office on October 8, 1979; at that time his vision, without correction, was 20/15 in the right eye and counting fingers at one to two feet in the left eye. New intraocular preretinal membranes, including a star fold, were present, with a new accumulation of subretinal fluid and redetachment of the retina in the left eye. In addition, increased cataract opacities were noted in the left eye.

At the patient's second admission to the hospital, on October 11, 1979, his best corrected vision was 20/25 in the right eye and light perception in the left eye, with intraocular pressure of 14 mm Hg in the left eye. The patient had massive periretinal proliferation syndrome with star folds in the retina which was responsible for redetachment of the retina in the left eye. On October 12, 1979, pars plana lensectomy, vitrectomy, and repair of the retinal detachment was carried out on the left eye. The operation was successful in that the retina was reattached and remained so for the entire hospital course; the patient was discharged on October 19, 1979.

The patient was seen in our office on October 29, 1979. At that time his vision in the right eye was 20/15; in the left eye his best corrected vision was in the 20/200 range with +13.00 diopter sphere. Intraocular pressure was 14 mm Hg in

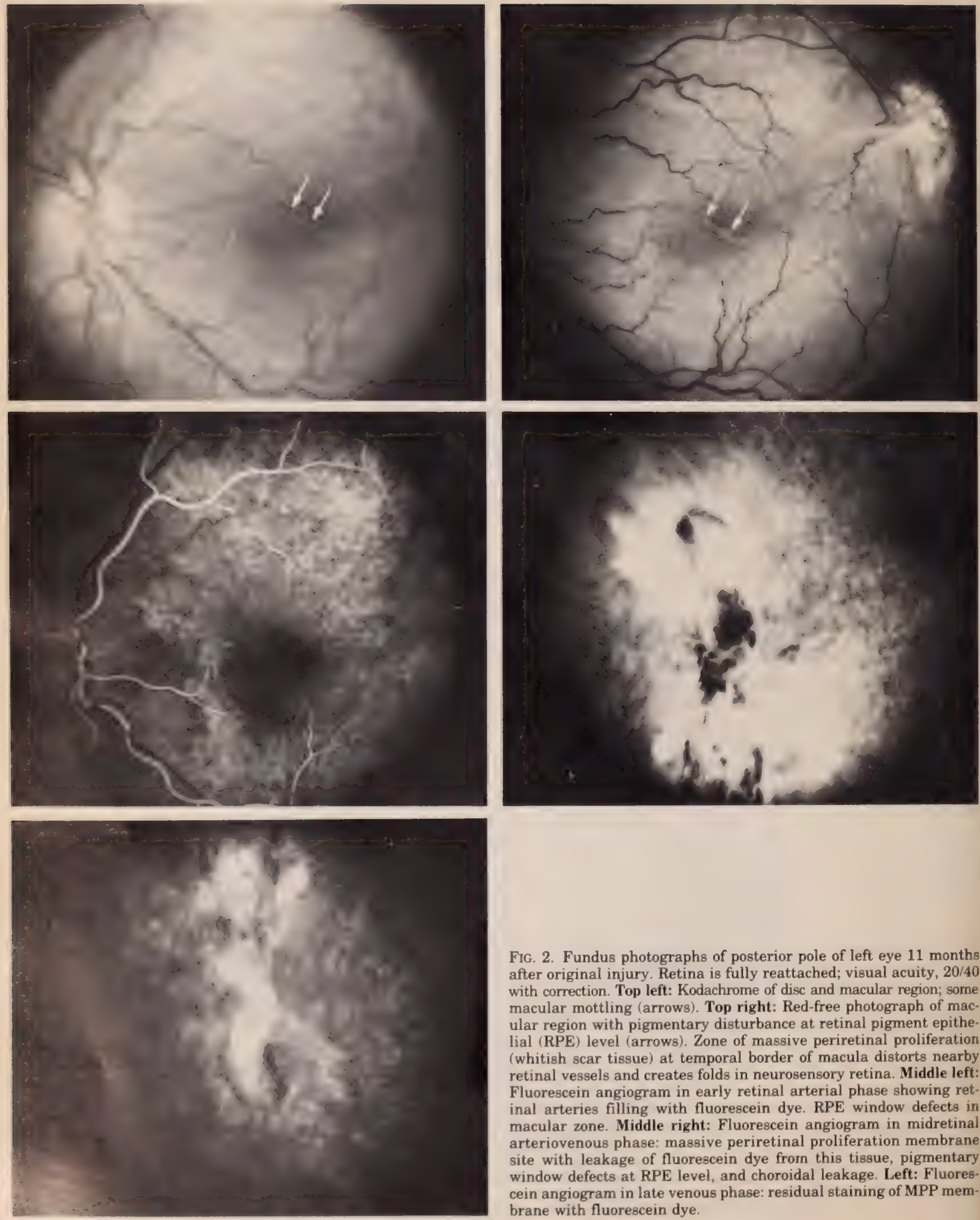

FIG. 2. Fundus photographs of posterior pole of left eye 11 months after original injury. Retina is fully reattached; visual acuity, 20/40 with correction. **Top left:** Kodachrome of disc and macular region; some macular mottling (arrows). **Top right:** Red-free photograph of macular region with pigmentary disturbance at retinal pigment epithelial (RPE) level (arrows). Zone of massive periretinal proliferation (whitish scar tissue) at temporal border of macula distorts nearby retinal vessels and creates folds in neurosensory retina. **Middle left:** Fluorescein angiogram in early retinal arterial phase showing retinal arteries filling with fluorescein dye. RPE window defects in macular zone. **Middle right:** Fluorescein angiogram in midretinal arteriovenous phase: massive periretinal proliferation membrane site with leakage of fluorescein dye from this tissue, pigmentary window defects at RPE level, and choroidal leakage. **Left:** Fluorescein angiogram in late venous phase: residual staining of MPP membrane with fluorescein dye.

the left eye by applanation tonometry. The retina appeared to be reaccumulating subretinal fluid, along with more preretinal membranes and a new retinal break in the center of a star fold (MPP membrane) located just superotemporal to the macula.

On the patient's third admission to the hospital, on November 12, 1979, he had vision of 20/20 in the right eye and best corrected visual acuity in the left eye of hand motion at half a foot. Intraocular pressures were 15 mm Hg in the right eye and 3 mm Hg in the left eye by applanation tonometry. The left eye was aphakic with massive periretinal proliferation syndrome, including new preretinal membranes and a new paramacular retinal tear. On November 13, 1979, the patient had a pars plana vitrectomy as well as cryopexy of the retinal break, along with intravitreal air-fluid-gas exchange to repair the retinal break and retinal detachment in the paramacular region of the left eye. This procedure resulted in complete reattachment of the retina.

The patient's postoperative course was excellent until eleven days postoperatively, when the eye began to reaccumulate subretinal fluid. The patient was informed of the reaccumulation of the subretinal fluid and was subsequently discharged on November 26, 1979.

The patient was then seen in our office on December 3, 1979 and his visual acuity, with correction, was 20/70 in the left eye. Intraocular pressure was 12 mm Hg in the left eye and all retinal tears appeared to be sealed, but there was still some residual subretinal fluid. The possibility of an exudative retinal detachment was considered because of these new findings and the fact that all retinal tears appeared to be sealed. A course of systemic steroids (prednisone 30 mg daily) was started for one week without any observable improvement in the subretinal fluid. Therefore the systemic steroids were discontinued.

In his next office visit on January 2, 1980, the patient's best corrected vision was 20/40 in the left eye with +12.25 diopter sphere $\supset$ +1.75 cylinder axis 45 degrees; the retina was attached and looked quite good. The patient's retina remained reattached and there was no regrowth of new intravitreal or preretinal membranes in his left eye. The patient did have some intermittent left exotropia but was able to fuse with a contact lens in position at near.

The patient's final visit to our office on August 13, 1980 revealed a best corrected (contact lens) visual acuity in the 20/40 to 20/50 range in the left eye. The macula appeared to be flat (Fig. 2). The rest of the retina was attached and appeared to be stable. Fluorescein angiogram on August 13, 1980 indicated good retinal circulation within the optic nerve head and macular regions (Fig. 2). There was, of course, staining with fluorescein dye at the site with MPP (star fold) and a previous retinal tear, which had been sealed with cryopexy treatment in the temporal macular region of the left eye.

Discussion

This case illustrates the inherent difficulties in managing patients with double perforating injuries to the globe that develop massive periretinal proliferation. The regrowth of the membranes, in this case, was responsible for the recurrent retinal detachments. A number of articles in the literature deal with the surgical management of these membranes (19–21); however, no known agents effectively inhibit the growth and development of intravitreal and retinal membranes, and so we are forced into surgical intervention. In this case, repeated surgical intervention was one key to the successful reattachment of the retina and restoration of vision. The other feature responsible for permanent reattachment of the retina was the spontaneous shutdown of the MPP cells. The reason for this remains obscure.

In other cases, repeated surgical intervention still may not be successful. It is clear that an agent that could biologically shut off the cells responsible for these MPP membranes would aid immeasurably in dealing with these complex cases of MPP.

Acknowledgments

I thank Laurel Cooke for her superb artwork on the illustrations.

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Submitted for publication August 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Radiologic Notes

Claude Bloch, M.D., and Harvey Peck, M.D., Coeditors

Metastatic Carcinoma Involving Paget Disease of the Bone: An Unusual Association

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Case Report. A 64-year-old white woman was transferred to The Mount Sinai Hospital for evaluation of a "hemolytic anemia." Her complaints at the time of admission were generalized bone pain, anorexia, weakness, and a 20-pound weight loss over seven months. She had "arthritis" since the age of 35. Paget disease of the bone was diagnosed at the age of 54. The patient was treated with analgesics and various anti-inflammatory agents. Three weeks prior to admission, treatment with prednisone (60 mg/day) was begun. Shortly thereafter, her reticulocyte count was elevated to 7.6% (0.5–1.5%) and she complained of easy bruisability.

Physical examination revealed an extremely obese patient with discomfort due to bone pain. Ecchymoses were present over the right forearm and left thigh. The liver edge was palpable 7.0 cm below the right costal margin. There was kyphoscoliosis and diffuse tenderness over the midthoracic and lumbar spine. Lower extremity muscular weakness was demonstrable. There were no joint abnormalities. The platelet count was 147,000 platelets/mm^3 (normal, 150,000–350,000 platelets/mm^3). The alkaline phosphatase was 655 mU/ml (normal, 30–110 mU/ml), gamma glutamyl transpeptidase 145 mU/ml (normal, 7–33 mU/ml), and the serum calcium determination was 10.4 mg% (normal, 8.5–11.0 mg%).

Skeletal survey documented extensive Paget disease. Roentgenograms of the thoracic spine showed diffuse indistinct trabeculation of the vertebrae, with evidence of localized destruction in areas involved by Paget disease (Fig. 1). Roentgenograms of the right scapula revealed a lytic lesion. A thin needle aspirate of the scapular lesion was performed for cytologic examination. Two weeks later, the patient developed abdominal pain, nausea, and a low grade fever and became hypotensive and lethargic. She died on the sixteenth day of hospitalization.

Diagnosis: Metastatic pancreatic adenocarcinoma in bone affected by Paget disease. The differential diagnosis includes sarcomatous changes of Paget disease, metastatic malignancy, disseminated malignant lymphoma.

Discussion. Cytologic examination of the thin needle aspirate of the right scapula demonstrated malignant cells.

At autopsy a moderately- to well-differentiated adenocarcinoma measuring 3.0 × 3.0 × 2.5 cm was found to occupy the tail of the pancreas. There were metastases to the head of the pancreas, regional lymph nodes, liver, lungs, atrial septum of the heart, ileum, adrenals, serosa of the uterus, and multiple bones (including the thoracic vertebrae, pelvis, ribs, and right scapula). Paget disease of bone was demonstrated in the pelvis and thoracic vertebrae.

All of the bones examined were dense and hard. The marrow cavities were extensively replaced by sclerotic yellow-tan bone. Within the marrow of the vertebral bodies and pelvis, this dense bone had focal areas of softening and necrosis. Firm white tissue occupied the marrow of the right

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scapula and ribs and invaded the surrounding soft tissues with destruction of the intervening cortical bone.

The primary pancreatic adenocarcinoma was a desmoplastic tumor consisting mostly of glands formed by tall columnar cells with ample clear pink cytoplasm and round to oval, basally oriented vesicular nuclei. Some glands were formed by cuboidal cells with hyperchromatic occasionally bizarre nuclei.

Histologic sections of the scapula and ribs showed metastatic desmoplastic adenocarcinoma replacing the marrow and destroying the cortex with invasion of the surrounding tissues. Sections of the pelvis and thoracic vertebrae showed marrow spaces filled with metastatic adenocarcinoma. The bony trabeculae were thickened and sclerotic; prominent cement lines in the characteristic mosaic pattern of Paget disease were intimately associated with metastatic adenocarcinoma (Fig. 2). Some osteoblastic bone formation was also found in association with metastatic tumor in some areas. There were no sarcomatous changes in any of the bones.

Although metastatic carcinoma in bone and Paget disease are relatively common conditions in the elderly, they have only rarely been described as occurring in the same bone (1, 2). The precise incidence of Paget disease of the bone is

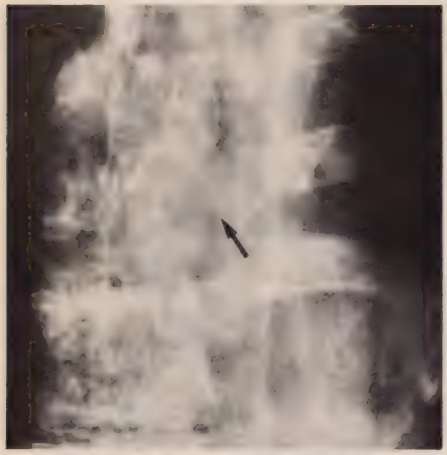
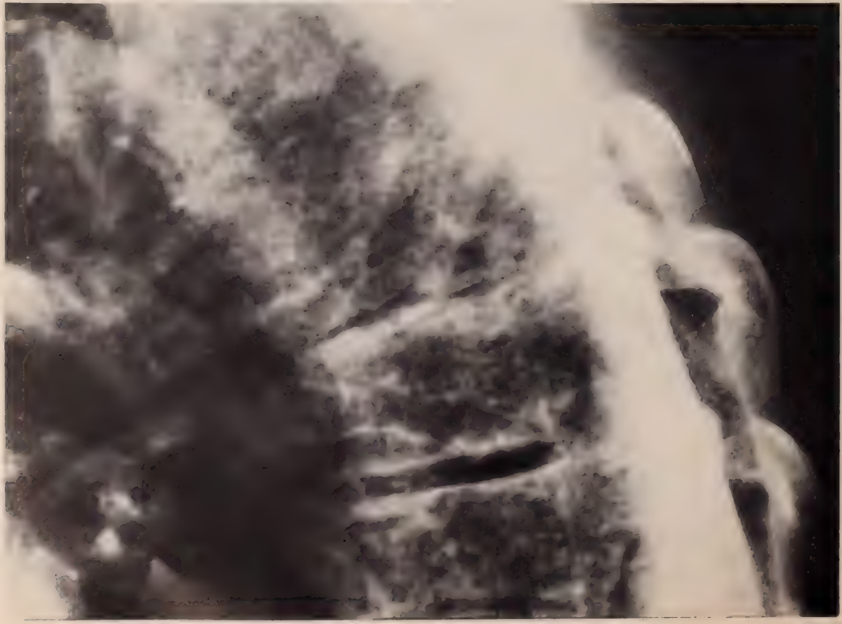


FIG. 1. Anterior posterior view (**left**) and lateral view (**below**) of thoracal spine; destruction of left pedicle of T_6 (arrow). Trabeculation of T_{7-8} is coarse and indistinct. Certain areas suggest Paget disease.



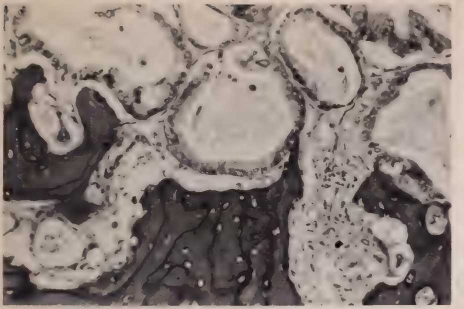


FIG. 2. Histologic section of 6th thoracal vertebra showing gland forming metastatic adenocarcinoma. Broad osseous trabeculae with prominent mosaic pattern is characteristic of Paget disease (hematoxylin and eosin, × 100).

not known. However, this condition was found in 138 (3.3%) of 4,614 consecutive autopsies of patients over 40 years of age (3). The incidence of malignant sarcomatous transformation in advanced Paget disease has been estimated at 10%–15% (4, 5).

The phenomenon of metastases to bones affected with Paget disease was first reported in 1956 by Castleman and McNeil (6). It has been suggested that the hypervascularity of the bone lesion in Paget disease may offer a good "soil" for implantation of malignant cell (2, 7). In view of the fact that both Paget disease and metastatic carcinoma are relatively common bone lesions of the elderly, it is not clear why their occurrence in the same bone has been documented so infrequently (1, 2, 6, 8). A recently published comprehensive treatise on metastatic lesions in bone briefly mentions the infrequent coincidence of the two conditions without offering any explanations (9).

The early radiographic changes of malignant sarcomatous transformation and metastatic deposits in Pagetoid bone are not easily distinguished from each other and include localized destruction, periosteal response, and tumor extension into adjacent soft tissue. The gradually growing mass and pain occasionally associated with a pathological fracture are the major clinical signs. When the lesion is localized, angiography and computerized tomography differentiate a benign from a malignant process (2). In diffuse involvement of the skeleton by both Paget disease and metastases, as in the case reported here, these procedures would not be helpful. The presence of Paget disease may divert the examiner's attention from a coexisting metastatic process when it is localized and confined within the bone with a relatively intact cortex.

There is a possibility that at the usual age of onset of Paget disease, when the lesion is hypervascular, malignant tumors which metastasize to bone are infrequent. Paget lesions may lose their activity and may no longer serve as a suitable environment for the deposition of circulating malignant cells in the advanced age group in which malignancies which would ordinarily metastasize to bone are more commonly encountered. Further observation and investigation should serve to clarify the true incidence of this supposedly rare association.

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Submitted for publication July 1983.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

Student's Corner

Howard Levin, Editor

Diffuse Histiocytic Lymphoma: Case Report

NEVILLE ALLEYNE, M.D.

Abstract

A case of diffuse histiocytic lymphoma in which the patient sought treatment for hoarseness, Horner's syndrome, and left cervical node enlargement is reported. The aggressive nature of this disease and its history, classification, and treatment are summarized.

Non-Hodgkin's lymphomas are malignant neoplasms of the lymphoreticular tissue which tend to occur about twice as frequently as Hodgkin's disease. Initial symptoms of the non-Hodgkin's lymphomas are usually localized or generalized lymphadenopathy, usually painless. The most common sites of nodal involvement are the anterior mediastinum and periauricular, epitrochlear, mesenteric, and Waldeyer's ring regions. Extranodal involvement occurs especially in diffuse histiocytic lymphoma with predilection for the stomach, small intestine, and pancreas. Not uncommonly, skin, bone, lung, and kidneys are initial presenting sites. However, hepatosplenomegaly with or without jaundice is rare as an initial feature.

The etiology of non-Hodgkin's lymphoma is unknown; however, good evidence implicates the Epstein-Barr virus as a causative agent in Burkitt's lymphoma seen in equatorial Africa. It is believed that other, not yet isolated oncogenic viruses may cause non-Hodgkin's lymphomas. Occupational exposure to asbestos or other mutagenic agents may be the impetus for a cascade of lymphoproliferative events which will develop into the disease. Cytogenetic alterations may be the cause, since patients with abnormalities in chromosome 14 show greater incidence of malignant lymphoproliferative diseases. Moreover, patients with genetic or acquired immunosuppression show a higher incidence of malignant lymphomas, including ataxia-telangiectasia, Wiskoff-Aldrich syndrome, congenital sex-linked agammaglobulinemia, and Chediak-Higashi syndrome.

Prior to the use of combined chemotherapeutic regimens and as late as the 1960s and early 1970s, the diagnosis of non-Hodgkin's lymphoma was usually associated with a very bleak prognosis. Today, however, many patients so diagnosed have high rates of remissions; some patients can be totally cured.

Thomas Hodgkin in 1832 was the first to describe, on post mortem inspection of seven cases, a cancer entity involving "absorbent glands and the spleen." In 1865, a second, larger series was reported by Wilk, who named it Hodgkin's disease (1).

In the early 1900s, Ewing described two distinct types of lymphomasarcoma, small-cell and large round cell, later called reticulum cell sarcoma. Brill in 1925 was the first to show that follicular lymphomas were very sensitive to radiotherapy; Symmers corroborated the findings of Brill in 1927 and named giant follicular lymphoblastoma Brill-Symmers disease. In 1958, Burkitt described a type of lymphoma among African children which seemed to have a propensity for involving the bones of the jaw and orbit along with the gonads (1). This tumor was later histologically found to have phagocytes with abundant cytoplasm, referred to as the "starry sky" pattern of Burkitt's lymphoma. The strong association of Epstein-Barr virus as an etiologic agent in Bur-

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This paper was written when the author was a third-year student at Mount Sinai School of Medicine.

kitt's lymphoma has been repeatedly documented.

Case Report. The patient was a 33-year-old white man with a history of diffuse histiocytic lymphoma diagnosed $2^{1}/2$ years before by cervical lymph node biopsy. He initially sought treatment for hoarseness, Horner's syndrome, and left cervical node enlargement.

He was treated with multiple courses of chemotherapy (doxorubicin hydrochloride, bleomycin, vincristine, Cytoxan, methotrexate, leucovorin rescue, and Ara-C) and a single course of radiation therapy to the chest.

Six months later, he developed fever of 102°F. and melena. Lymphomatous infiltration of the jejunum at the ligament of Treitz was suspected. As a result, he was given another trial of combined chemotherapy with Ara-C, methotrexate, and leucovorin rescue. The upper gastrointestinal bleeding was managed conservatively with antacids and cimetidine.

About two weeks later, he had symptoms of small bowel obstruction. At this time, his bone marrow was depressed and he had an acute abdomen. He was treated with prednisone, methotrexate, and leucovorin rescue; however, radiotherapy was ruled out because of his bone marrow suppression. The patient improved until eighteen months; two days prior to admission he began noticing acute periumbilical pain relieved by passage of gas and anorexia. One day prior to admission he developed fever of 102°F. with rigors, night sweats, cough productive of white sputum, and diffuse lower abdominal pain.

In the hospital the patient was treated with intravenous antibiotics and responded well. He was discharged on a regimen of oral prednisone 160 mg/day, Mylanta, α-methyl-dopa, and cimetidine.

He was doing well until twenty-two months from first date; six days prior to admission he experienced acute severe abdominal pain. He was brought to the emergency room, where a diagnosis of perforated viscus was made on clinical and radiographic findings. He was treated with intravenous antibiotics, including aminoglycoside, clindamycin, and cephalosporin; emergency exploratory laparatomy revealed extensive involvement of the proximal jejunum and left colon. Resection of the involved organs with restoration of small-bowel continuity by a duodenojejunostomy and end colostomy were performed. He remained on triple antibiotic therapy and intravenous cortisol after surgery. One week postoperatively he developed a gastrocutaneous fistula and bouts of hematemesis. Bleeding resulted in several bouts of hypotension. As a result, 15 units of whole blood were transfused during the three-week postoperative course. In light of rapidly advancing disease unresponsive to combined chemotherapy, reoperation was not considered. He died twenty-three months from first date, after a brief episode of coma, hypotension, and hemorrhagic shock.

Discussion

Recent advances in the treatment of non-Hodgkin's lymphoma dictate that exact histologic classification and staging for the disease be made. Rappaport was the first to classify the non-Hodgkin's lymphomas into morphologic groups. The Rappaport classification separates non-Hodgkin's lymphomas into two major categories, nodular and diffuse. Nodular lymphomas are further subdivided into lymphocytic, poorly differentiated (LPD); mixed lymphocytic-hystiocytic (ML-H); histiocytic (H). Diffuse lymphomas are further subdivided into lymphocytic, well differentiated (LWD); lymphocytic, poorly differentiated (LPD); mixed lymphocytic-histiocytic (MLH); histiocytic (H); undifferentiated non-Burkitt's type (UNB); and undifferentiated Burkitt's type (UB).

Other classifications of non-Hodgkin's lymphomas include the Dorfman, Bennett, Kiel, and Lukes-Collins systems (2). Most prefer the traditional Rappaport classification, but a 1977 study by Warnke et al indicated that in the Rappaport system, nodularity does not influence survival. Those who are familiar with the Rappaport classification do not hesitate to point out that if the lymphoma is nodular, the patient's prognosis is better than if it were diffuse. Limitations of the Rappaport classification are primarily related to the basing of the system on histologic architecture and not on immunologic characteristics of the lymphoma. With greater accuracy in classification of the non-Hodgkin's lymphomas, treatment will increase the rate of remission and overall cure for this devastating disease.

In 1972 and 1975, eight patients with diffuse histiocytic lymphoma were treated with combined chemotherapy, including cyclophosphamide, vincristine, methotrexate, leucovorin rescue, and cytosine arabinoside at Yale University. Of these eight patients, six achieved complete remission and five had a five-year relapse-free period (3). It is thought that patients remaining relapse-free for two years appear to be cured of their disease. To treat non-Hodgkin's lymphoma properly, accurate clinical and pathologic staging is required. Patients with stage I or

I_E disease are usually treated with high-dose radiation therapy. Those with clinical stage II, III, or IV disease should receive combined chemotherapy. If an abdominal mass can be localized, additional radiation therapy or surgical debulking is most advantageous. The most effective combined chemotherapies to date for non-Hodgkin's lymphoma are (3):

C-MOPP (cyclophosphamide, Oncovin, procarbazine, prednisone).

CHOP/HOP (cyclophosphamide, doxorubicin, Oncovin, prednisone/doxorubicin, Oncovin, prednisone).

COMLA (cyclophosphamide, Oncovin, methotrexate, leucovorin, cytosine arabinoside).

BACOP (bleomycin, cyclophosphamide, Oncovin, prednisone, doxorubicin).

Those patients who do not respond to any of these primary induction protocols are unlikely to survive their disease.

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Submitted for publication September 1982.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 50, No. 6, November–December, 1983
Printed in U.S.A.

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